misunderstanding, then they instead misrepresented the articles under discussion.

Also, OSHA claims that "data suggest that sidestream smoke may contain more carcinogenic activity per milligram of cigarette smoke condensate than does mainstream smoke," citing to Ex. 3-689D. The exhibit available to the public was not labeled in such a way that Part "D" could be identified. This made it difficult to assess the reference for OSHA's claim.

In discussing Otto and Elmenhorst's paper (Ex. 8-247), OSHA states that this research has "shown that there are carcinogenic constituents in the vapor phase of tobacco smoke." Contrary to OSHA's assertion, the authors write: "the conclusion seems justified that tumor-inducing factors must be in the particle-phase of the smoke" [emphasis added]. The authors also indicate, in the summary of the study, that their chronic exposure regimen "had no significant effect on the spontaneous tumor-rate." Thus, this study, even given OSHA's misrepresentation of its conclusions, in no way supports OSHA's claim that the "carcinogenicity" of tobacco smoke has been shown in animal experiments.

Leuchtenberger and Leuchtenberger (Ex. 8-197) used neither ETS nor sidestream smoke as a surrogate for ETS. According

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to their paper, they used "whole fresh cigarette smoke" or "its gas phase alone." The Leuchtenberger article is not an chronic inhalation study of ETS or sidestream smoke, as implied in the preceding paragraph. The results cited by OSHA (pulmonary adenomas and adenocarcinomas in male mice) are but one aspect of the data reported in the study. The authors comment that those changes could be found in control animals at a later age and lower frequency. The authors note that "chronic inhalation of the gas phase of fresh cigarette smoke did not evoke bronchogenic carcinoma" [emphasis added]; they also indicate that no bronchogenic carcinomas were observed in mice exposed to whole fresh smoke. Thus, the data from this study do not support OSHA's position.

Harris, et al., (Ex. 8-135) is correctly acknowledged as a mainstream smoke study by OSHA. With regard to their reported results, the authors stated that "spontaneous" tumors appeared in their control animals during the course of their chronic study, and said that "it would no longer be accurate to refer to the inhaled smoke:air mixtures as the cause of these tumors but merely as eliciting a higher incidence." Thus, according to the authors themselves, this study's data do not support a determination that cigarette smoke causes lung cancer in experimental animals.

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In Mohr and Reznik (Ex. 8-226), one of the references cited by OSHA to support the statement "Studies have also reported hyperplasia and metaplasia in the trachea and bronchi of mice exposed to cigarette smoke by the inhalation route," the variability of the results reported from smoke inhalation studies is discussed. More importantly, Mohr and Reznik write:

> [T]he majority of investigations in tobacco smoke research have been conducted by some form of inhalation technique. . . . Nevertheless, no researcher has succeeded as yet in producing a significant incidence of pulmonary tumors. (p. 347) [emphasis added]

Thus, in its selective treatment of these data, OSHA uses a lengthy review paper to support a single statement. However, OSHA fails to discuss the concluding statements made by the authors of that review. Arguably, the most important point in this review paper is what the authors noted above: that animal inhalation studies using tobacco smoke have not reported a significant increase in pulmonary tumors in exposed animals. This statement casts doubt over all of OSHA's contentions that animal inhalation experiments support the claimed carcinogenicity of ETS.

In the discussion of a paper by Davis, et al. (Ex. 8-79), which again deals with chronic exposure to vapor-phase smoke, not sidestream smoke or ETS, OSHA presents the data in such a way that

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the paper's lack of a statistically significant result is effectively obscured. While OSHA's statement that: "Pulmonary squamous neoplasms were detected in female Wistar rats exposed to a 1:5 smoke-to-air mixture . . ." is not actually incorrect, it implies that the tumors were found only in exposed animals.

If one reads the conclusion of the paper cited, the following statement is found:

> The results provide convincing evidence that, under the conditions of the experiment, exposure to VP did not increase the incidence of any kind of neoplasm at any body site. (p. 467) [emphasis added]

The authors also note that cellular changes in the respiratory tract were no more frequent in exposed rats than in control rats.

While OSHA does make an accurate statement (i.e., that neoplasms were produced), its failure to present the complete picture, namely, that neoplasms were reported no more frequently among exposed than unexposed animals, is deceptive and misleading. The data presented in this paper do not support claims that animal inhalation studies show carcinogenic effects of tobacco smoke inhalation.

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Some of the papers cited by OSHA, in this section which focuses on lung cancer, present data on tumors of sites other than the lung. Studies of this sort provide limited information pertinent to the issue at hand, namely, lung cancer. For instance, Dalbey, et al. (Ex. 8-77), reported a large number of benign adenomas or nasal tumors in chronically-exposed rats. Similarly, Dontenwill (Ex. 8-88) actually commented on the "very rare appearance of lung carcinomas" in his chronic inhalation study of hamsters (only 1 case).

Bernfeld, et al. (Ex. 8-30) reported on laryngeal changes, not changes to the lungs or bronchi. Moreover, the authors indicated that responses to chronic smoke inhalation varied greatly between the two hamster strains tested. If, then, two strains of the same species can exhibit markedly different responses in an experiment, by combining strains and species in the discussion and not considering the unique biology of the different animals tested, OSHA displays a overly simplistic view of biology.

In the discussion of the Auerbach, et al. (Ex. 8-19) study, in which dogs smoked through a tracheostomy, that is, a tube inserted into a hole cut into the animal's trachea (windpipe), OSHA did not even note that the Auerbach study used the tracheostomy method, as opposed to the exposure chambers used in the majority of the other studies discussed. More importantly, OSHA did not

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address the inappropriateness of this route of exposure to either active smoking or ETS.

The Mohr and Reznik review (Ex. 8-226), cited by OSHA and discussed here previously, contains the following statements about the use of the tracheostomy method:

> [M]ost importantly, smoking through a tracheostomy is a highly artificial system and bears little resemblance to human experience. This is particularly the case when it is remembered that the normal dilution of smoke air is not achieved by this technique, with the result that the concentration of smoke is much higher than if taken in through the mouth.
>
> The most positive results have been obtained by means of tracheostomies in dogs. However, once again the extreme artificiality of this system prevents any real correlation of the obtained experimental results to humans. (p. 347) [emphases added]

Mohr and Reznik are discussing the relevance of data obtained in tracheostomy data to active smoking in humans. The relevance of these data to OSHA's Proposed Rule is certainly questionable, particularly given the extreme dilution of ETS once it is in room air.

Studies such as Grimmer, et al. (Ex. 8-127), discuss direct pulmonary implantation, in which a beeswax solution, containing a substance to be tested (here, condensed particles and

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semivolatiles from sidestream smoke), is injected into the animal's lungs. The relevance of this experimental route of exposure in comparison to inhalation exposure is unclear. Moreover, the authors of the paper fail to present analyses of the statistical significance of their reported results. It is thus not possible to evaluate whether the paper supports OSHA's claims.

Dagle, et al., (Ex. 8-75) and Stanton, et al., (Ex. 8-289) report on the injection of a pellet of beeswax containing cigarette smoke condensate into the lungs of rats. Theoretically, this pellet would approximate chronic exposure, as substances "leach" from the pellet over time. However, as the authors of Ex. 8-289 note: "A major disadvantage is the unnatural exposure of respiratory epithelium to the carcinogen." Also, both these studies report simply on the development of this technique for bioassays.

In the subchronic study of Coggins, et al. (Ex. 8-59), aged and diluted sidestream smoke was used as a surrogate for ETS. This substance may be a more appropriate approximation of ETS than are other forms of tobacco smoke. While OSHA provides a factual summary of the conclusions of this study, they fail to note that effects (hyperplasia and inflammation) were reported only in animals exposed to particle concentrations some 100 times higher than typical real-world concentrations. Coggins, et al. (Ex. 8-60)

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also report the same minor, completely reversible histopathological changes. The changes did not progress over longer periods of exposure, and once again occurred only at particle concentrations some 100-fold higher than real-world levels.

In a 14-day inhalation study, one would not expect lung tumors to develop. Thus, the relevance of the work of Coggins, et al., to OSHA's discussion of cancer is limited. Nevertheless, Coggins, et al. show only minor, reversible cellular changes following intense exposure to a surrogate for ETS.

At 59 FR 15981, OSHA cites to a book by Wynder and Hoffmann (Ex. 8-327) (the citation is unclear, particularly with respect to page numbers, as it is not a chapter or even a definable section), discussing "skin-painting" studies in which tobacco tar condensates were applied to mouse skin. In the very book cited, the authors write:

> The bioassay[s] for tobacco products on mouse epidermis have not answered questions on the problem of respiratory carcinogenesis. (p. 145)

Thus, the relevance of mentioning skin-painting studies in this context is unclear.

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Reif, et al. (Ex. 8-259) reports on a "case-control" study in which owners of dogs that had died of lung cancer were asked about the dogs' exposures to ETS. Risk estimates for the dogs' developing lung cancer were then calculated. The study's authors note:

> The current study suffers from some of the same limitations found in the studies done in humans, i.e., small sample sizes, imprecise risk estimates, and difficulties in measuring exposure. (p. 238)

The "risk estimates" reported in this study were not statistically significant. Thus, these data in no way support the claim of an association between ETS exposure and lung cancer risk.

Not only do the data cited by OSHA fail to support OSHA's claims, but they represent a troubling approach to science. OSHA's Proposed Rule should be accurate and balanced: the complete data should be presented fairly, whether or not they support OSHA's position. To the reader unfamiliar with OSHA's process, misrepresenting data gives the impression that OSHA is using those data to achieve a predetermined conclusion, or that the staff responsible for the Proposed Rule did not understand the material reviewed.

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OSHA's discussion of animal studies omits certain references concerning inhalation studies

Despite the fact that data from subchronic animal inhalation studies are of minimal relevance to the question of whether animal data support claims of the "carcinogenicity" of ETS, OSHA nevertheless chose to include some subchronic studies in its discussion. However, OSHA omitted several studies, which, in the interest of completeness, are described below. None of the studies report data supporting any permanent changes following subchronic exposure of animals to sidestream smoke at levels exceeding those encountered in "real-life" situations.

Haley, et al., 1987a, 1987b

Preliminary reports on this American Health Foundation study, in which hamsters were exposed to mainstream or sidestream smoke 7 days/week for 18 months, are available;[52,53] apparently, however, no final report has been published. In those reports, the authors note that smoke-exposed animals were living longer than were sham or cage control animals. No additional information was presented.

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von Meyerinck, et al., 1989

Rats and hamsters of both sexes were exposed to sidestream smoke at a concentration of 4 mg/m^3 TPM and 25-30 ppm carbon monoxide for 10 hours/day, five days/week for 90 days.[54] The authors noted about their exposure system: "The levels in the exposure chamber were at least 1 and in some instances 2 orders of magnitude higher than reported for smoke-polluted rooms under real-life conditions." (Elsewhere, the authors described these conditions as "unrealistically high."[55]) One hundred animals of each species were exposed, 115 of each species were sham controls, and 100 of each species were room controls. The authors reported minor, completely reversible histopathological changes in the nasal cavity in rats only, and no alterations in any other part of the respiratory tract.

Teredesai and Pruehs, 1994

Male rats and male hamsters were nose-only exposed to fresh sidestream smoke (FSS) for seven hours/day, seven days/week for 90 days.[56] One group of 20 animals was exposed to FSS with a total particulate matter (TPM) concentration of 2 ug/L, one to FSS with TPM of 6 ug/L, and one served as a sham exposure group. Histopathological changes described as "slight" were reported in the nose and larynx of exposed rats, "mainly in the high FSS

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concentration group." These changes were reversible following cessation of exposure. The authors noted that "[n]o smoke-exposure-related histopathological changes were observed in trachea and lungs."

Thus, these additional studies not referenced by OSHA fail to support claims that animal data support the purported carcinogenicity of ETS.

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SECTION VI

MATERIAL IMPAIRMENT: CARDIOVASCULAR DISEASE

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CARDIOVASCULAR DISEASE

Introduction

This submission is set forth in two parts. Part I provides a critical evaluation of the claims and literature cited by OSHA in its Proposed Rule on the issue of ETS exposure and cardiovascular effects. Part I concludes that OSHA has not provided an adequate scientific foundation for its position that ETS exposure in the workplace increases the risk of adverse cardiovascular effects. Of particular importance is that OSHA has not based its position on the best available evidence, namely those epidemiological studies that actually attempted to estimate workplace ETS exposure in relation to heart disease risk. The best available evidence does not support a claim that workplace ETS exposure is associated with an increase in heart disease risk.

Part II provides a compilation of literature which raises questions about whether ETS exposure is associated with adverse cardiovascular effects. Most of this literature, despite its importance and relevance, was not even cited by OSHA. The literature in Part II includes conclusions from several major reviews. It also includes reports on several specific areas discussed incompletely or inadequately in OSHA's comments on cardiovascular disease. These areas include discussions of the extremely low levels of ETS or of ETS constituents to which

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nonsmokers might be exposed, as well as reports discussing research suggesting that any measurable cardiovascular responses to ETS are minor.

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Part I: Response to Specific OSHA Claims

OSHA HAS NOT PROVIDED AN ADEQUATE SCIENTIFIC FOUNDATION FOR ITS POSITION THAT ETS EXPOSURE IN THE WORKPLACE INCREASES THE RISK OF ADVERSE CARDIOVASCULAR EFFECTS

The major discussion of cardiovascular effects in OSHA's Proposed Rule is provided at Section II.C.4. (59 FR 15977) The following discussion relates primarily to that section, although other portions of the notice are addressed as well, when warranted by their relevance to cardiovascular disease claims.

OSHA argues that research indicates that ETS exposure has a variety of adverse cardiovascular effects, including both acute effects, relating especially to oxygen supply and demand, and chronic effects, such as atherosclerosis and increased risk for the development of and death from coronary heart disease.

OSHA does not provide adequate support for its claim that ETS in the workplace should be regulated because of an association between ETS exposure and adverse cardiovascular effects. Much of the supporting literature cited by OSHA deals with active smoking, not ETS. Other studies, even though they may deal with ETS, are so flawed and limited in scope that they do not provide a sound basis for cardiovascular disease claims. Perhaps most importantly,

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actual workplace data on ETS and heart disease are scant. Such data as exist do not support an association between workplace ETS exposure and cardiovascular disease.

OSHA DOES NOT BASE ITS CONCLUSIONS CONCERNING WORKPLACE ETS EXPOSURE AND HEART DISEASE RISK ON THE BEST AVAILABLE EVIDENCE. BASED ON THE BEST AVAILABLE EVIDENCE, WORKPLACE ETS EXPOSURE HAS NOT BEEN ASSOCIATED WITH A STATISTICALLY SIGNIFICANT INCREASED RISK OF HEART DISEASE.

Since OSHA's proposed rulemaking relates to the workplace, the best available evidence it should consider on the issue of heart disease risk and ETS exposure is that based on the workplace, not on residential exposure or spousal smoking. Of the epidemiological studies cited by OSHA relating to ETS and heart disease, three studies provided data on workplace exposure. These are: Dobson, et al. (Ex. 8-85); Lee, et al. (Ex. 8-191); and Svendsen, et al. (Ex. 8-295). Each of those reports provided estimates of the relative risk for heart disease mortality associated with workplace ETS exposure. The studies were consistent in not reporting a relationship of workplace ETS exposure with heart disease. Therefore, based on the best available evidence, the literature does not support OSHA's claim that workplace ETS exposure is related to heart disease in nonsmokers.

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The three workplace studies are discussed more fully below.

Dobson, et al. (1991)

Dobson, et al., was a case-control study of myocardial infarction and heart disease mortality, which included questionnaire data relating to coworker smoking as an estimate of workplace ETS exposure. Odds ratios, with 95% confidence intervals, for workplace ETS exposure were reported as follows: 0.95 (CI: 0.51-1.78) for men and 0.66 (CI: 0.17-2.62) for women. Based on these data, Dobson, et al. concluded that the "odds ratios for passive smoking at work did not suggest increased risk."

Lee, et al. (1986)

Lee, et al., reported a hospital-based case-control study in which, in addition to information on spousal smoking, ETS exposure was estimated by asking the subjects about the extent to which they were exposed to ETS in four situations: at home, at work, during daily travel and during leisure time. Using a numerical index which combined questionnaire responses on ETS exposure in each of these situations, Lee, et al., reported relative risks of 0.52 (for lower combined exposure) on 0.61 (for higher combined exposure). Lee, et al, did not provide confidence

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intervals, but stated that none of these risks ratios were statistically significant.

Svendsen, et al. (1987)

This study, although it primarily used spousal smoking as the estimate of ETS exposure, also included a small amount of information regarding workplace ETS exposure, as estimated from questionnaire data relating to smoking by coworkers. Comparing nonsmokers whose coworkers smoked to nonsmokers whose coworkers did not smoke, the following relative risks, with 95% confidence intervals, were reported for heart disease. For coronary heart disease mortality, the relative risk reported was 2.6 (CI: 0.5-12.7) and for fatal or nonfatal coronary heart disease combined, the relative risk reported was 1.4 (CI: 0.8-2.5). The wide confidence intervals include 1.0 and are, therefore, not statistically significant.

In sum, the best available evidence does not support the claim that workplace ETS exposure is associated with an increased heart disease risk. None of the three epidemiological studies cited by OSHA that include workplace data on ETS exposure and heart disease report a statistically significant association. Moreover, the relative risks in two of these studies are less than 1.0 (relatively fewer deaths in the ETS exposed workers).

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OSHA provides inadequate support for its claims about ETS exposure and thrombus formation

OSHA addresses the issue of thrombus formation in the Proposed Rule at Section II.C.4.(a). (59 FR 15977)

OSHA argues that ETS exposure is involved in the formation of blood clots. OSHA cites only two laboratory studies to support this claim. Both of these studies focused on platelet activity. In one of these, Burghuber, et al. (1986) (Ex. 8-40), examined platelet function in a group of only nine nonsmokers, following a single exposure to high levels of ETS. The relevance of this artificial, short-term laboratory procedure to actual workplace conditions is highly speculative. Furthermore, these authors acknowledged that their test for platelet function in the laboratory may have no relevance to how platelets act in real life. They stated: "However, as with other platelet function tests, we do not know if this **in vitro** procedure accurately reflects platelet function **in vivo**." (p. 37) The authors further acknowledged that it was not known whether their research had implications for cardiovascular function in ETS-exposed nonsmokers. They stated: "Further investigation is needed to elucidate whether this finding is important with respect to a possible increased incidence of thromboembolic disease among non-smokers passively exposed to cigarette smoke." (p. 37)

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In another laboratory study cited by OSHA on ETS exposure and platelet function, Davis, et al. (1989) (Ex. 8-80), reported that 20 minutes of exposure to ETS increased platelet aggregation and also increased the number of endothelial cell carcasses in the blood. However, this was a highly limited study of only 10 male subjects, for which there was no true control condition. More specifically, in their exposure condition, the nonsmokers sat for 20 minutes in a hospital corridor where patients typically smoked. Not only does this constitute an imprecise ETS exposure, but it is not comparable to the control nonexposure condition. In the nonexposure condition, the nonsmokers sat in a laboratory where smoking was not allowed. A hospital corridor and a hospital laboratory are entirely different environments, involving potential confounding factors such as social conditions, noise factors, ventilation factors and a variety of other differences.

Other than the two laboratory studies, the only other citation with ETS data cited by OSHA was a 1991 report by Dobson, et al. (Ex. 8-85) This epidemiological study, in addition to reporting odds ratios for ETS exposure and heart disease, also provided data on fibrinogen concentrations. However, Dobson, et al. repeatedly noted that there was no statistically significant association of fibrinogen concentration with ETS exposure. Moreover, limitations of this study were explicitly acknowledged by the authors, thus making this paper unreliable as a basis for

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OSHA's claims. For example, Dobson, et al. noted that there were "[d]ifferences in the methods of data collection and truthfulness in reporting smoking habits" between their exposed and nonexposed groups and that this might "have lead to bias." (p. 796) The potential effects of confounding factors, especially socioeconomic status, were noted, as well as the lack of statistical power in their study. In general, with regard to their epidemiological procedure, which was the basis for both the odds ratio and fibrinogen data, Dobson, et al. stated: "On balance, the effects of bias and confounding could have lead to overestimation of risks due to passive and active smoking." (p. 796)

Other citations listed in OSHA's review of the thrombus formation issue are not relevant to ETS. Some merely provide background or theoretical information concerning cardiovascular disease processes. (e.g., Exs. 8-111, 8-272) Others are studies of active smoking, not ETS. (Exs. 8-157, 8-224)

OSHA fails to adequately support its claim that ETS exposure is associated with vascular wall injury

OSHA addresses the issue of vascular wall injury in the Proposed Rule at Section II.C.4.(b). (59 FR 15977)

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OSHA argues that ETS exposure may harm the endothelial lining of the arterial wall, but provides almost no support for this claim. In connection with this claim, OSHA refers to only one citation -- namely, the Davis, et al. (1989) report (Ex. 8-80), which, as noted in the previous section regarding thrombus formation, is a highly limited and flawed study.

OSHA's discussion of possible mechanisms of effect is not adequately supported; some of the cited references are irrelevant to this issue

OSHA addresses the issue of possible mechanisms of effect primarily in the Proposed Rule at Section II.C.4.(c). (59 FR 15977) Part of OSHA's discussion of risk assessment in Section IV.F.2, which addresses cardiovascular effects in relation to pharmacokinetic modeling, is also germane.

In Section II.C.4.(c), OSHA argues that there are three mechanisms by which ETS exposure "may place stress on the heart." The first mechanism is by decreasing myocardial oxygen supply. The primary manner in which ETS exposure theoretically might have this effect, as discussed by OSHA, is via formation of carboxyhemoglobin. OSHA cites only one study on this issue which actually involved ETS. This was a 1978 report by Aronow. (Ex. 8-13) The Aronow study is widely regarded in the scientific literature as being methodologically weak and unsubstantiated.

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Furthermore, it is important to note that Aronow has been criticized severely for unethical and dishonest scientific practices, to the extent that the government no longer relies on his data. (Shephard, R., The Risks of Passive Smoking, London, Croom Helm Ltd., 73, 1982.) (Mintz, M., "FDA, Citing Phony Evidence, Bars Drug Tests by Researcher," The Washington Post, March 23, 1983.) (Peterson, C., "EPA Probe Criticizes a Study Used in Air-Quality Standard," The Washington Post, June 7, 1983.)

Although OSHA cites several additional reports in the context of discussing oxygen supply and demand (Exs. 8-242, 8-323, 8-324), these are reports on cigarette smokers, not of nonsmokers exposed to ETS.

The second mechanism for placing "stress on the heart" mentioned by OSHA is that oxygen demand may be increased via nicotine. However, OSHA does not provide any citations demonstrating that there is an association of ETS exposure with myocardial oxygen demand, much less an association with an increased demand specifically as a result of nicotine in ETS. Perhaps there is a theoretical argument, based on claims that nicotine is a pharmacological stimulant, for speculating that ETS may be associated with increased oxygen demand. Such an argument, however, does not recognize that the amounts of nicotine in ETS are extremely small and of doubtful physiological or cardiovascular

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relevance. [See Part II.B. of this submission for examples of literature, ignored or not adequately addressed by OSHA, which relates to the minute levels of ETS, and of ETS constituents, to which nonsmokers might be exposed, and the doubtful cardiovascular significance of such exposure levels.]

The third mechanism discussed by OSHA is that ETS exposure may influence the cellular ability of the heart to utilize oxygen for energy production. The only citation on this point provided by OSHA is Ex. 8-123, which OSHA describes as a study demonstrating that healthy subjects became fatigued quicker when exercising in the presence of ETS. However, OSHA's description of Ex. 8-123 is incorrect. Ex. 8-123 is not a study of exercise performance and ETS. It is not even a research report with original data. It is merely a draft of a review paper by Stanton Glantz and William Parmley. In one section of their draft manuscript, Glantz and Parmley discuss an exercise study involving healthy subjects and ETS. This 1985 study by McMurray, et al. is elsewhere referenced by OSHA as Ex. 8-217. However, the McMurray, et al. report does not provide direct measurements of cellular oxygen utilization. Thus, it does not bear importantly on the issue for which OSHA cited it.

An additional heart disease mechanism proposed to be related to ETS is suggested by OSHA in Section IV.F.2., where

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cardiovascular physiology is discussed in the context of pharmacokinetic modeling of ETS exposure. In Section IV.F.2., in addition to carbon monoxide and nicotine, OSHA proposes that polycyclic aromatic hydrocarbons (PAHs) have been associated with cardiovascular effects. To support this claim, OSHA cites the draft manuscript by Glantz and Parmley (Ex. 8-123), which presents no original data. It references several reports primarily dealing with injections of massive amounts of PAHs into chickens and pigeons. Given the doses and manner of administration, it is highly questionable whether this type of study has implications for any sort of inhalation exposure related to tobacco smoke, whether active smoking or ETS exposure.

OSHA's discussion of acute heart effects relies heavily on studies of questionable validity and fails to accurately represent the conclusions of some reports

OSHA addresses the issue of acute heart effects in the Proposed Rule at Section II.C.4.(d). (59 FR 15977-8)

In this section, OSHA argues that ETS exposure has certain acute effects, such as raising CO levels in the blood, increasing heart rate and blood pressure and affecting blood components that may be involved in atherosclerosis. Much of this section duplicates the claims in OSHA's immediately preceding

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section on "Possible Mechanisms of Effect." OSHA again relies strongly on highly flawed studies, in particular, the 1978 Aronow study (Ex. 8-16, which is the same as Ex. 8-13) and the studies on platelets by Burghuber, et al. (Ex. 8-40) and Davis, et al. (Ex. 8-80).

One of OSHA's central points in this section is that exposure to ETS results in a significant increase in carboxyhemoglobin. It is odd that, in introducing this topic, OSHA cites the review and conclusions of the National Research Council (1986). In fact, the NRC report concluded that if background air has little or no carbon monoxide, then even upper estimates of what might be produced from ETS would "have a negligible effect on carboxyhemoglobin levels." (p. 128) Furthermore, the 1986 Surgeon General's Report, in addressing this same issue, concluded as follows: "Thus, small increments of carbon monoxide due to environmental tobacco smoke may be indistinguishable from that due to endogenous and non-tobacco-related sources." (p. 202)

OSHA also incorrectly describes that data in Guerin, et al. (Ex. 8-129) as indicating that it is common for workplace ETS exposure to be associated with significant increases in COHb levels. In point of fact, Ex. 8-129 concludes the opposite, noting that "studies which quantified the percentage COHb in nonsmokers show very little difference in nonsmokers who were or were not

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exposed to ETS." (p. 160) Elsewhere in Ex. 8-129, a similar conclusion is reached, noting that nearly all CO in indoor environments arises from sources other than ETS.

> CO has been measured repeatedly in rooms where there is adequate ventilation, with and without cigarette smoking. In many cases, the difference in values is small, and is easily masked by either normal variation in the data or the precision of the analytical measurement. Studies which measure the concentration of COHb in both ETS-exposed and non-exposed subjects is consistent with environmental CO measurements, and have demonstrated no consistent significant differences in most indoor environments. The chief difficulty is interferences from other sources of CO, particularly cooking, heating, and vehicle exhaust. One author (Eatough, 1988) states that about 90% of all CO arises from sources other than ETS. (p. 177) (Ex. 8-129)

Other literature cited by OSHA in this section also does not provide substantial support for, and sometimes is, at best, remotely relevant to OSHA's claims of acute cardiovascular responses to ETS. For example, OSHA cites Ex. 3-38 to support its claim that ETS has acute effects in angina patients. However, Ex. 3-38 consists of materials from the state of Washington, Department of Labor and Industries, relating to a proposed indoor air regulation. It has no apparent relevance to the context in which OSHA cited it. On the same point, OSHA cites Milhorn (1989). (Ex. 8-222) But Milhorn (1989) is not a study of ETS. It is

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primarily a review of behavioral issues related to nicotine, as they might be relevant to physicians' advice to their patients about smoking.

On the issue of potential cardiovascular responses in healthy people, OSHA cites Asano, et al. (1985) and McMurray, et al. (1985). (Exs. 8-18 and 8-17) Although these articles report minor changes in certain cardiovascular variables, such as heart rate, it is doubtful whether these have any physiological significance, even assuming that such responses were actually direct responses to ETS, rather than reflective of a psychological reaction to ETS exposure.

In supporting its claim that ETS exposure has acute effects on blood components, OSHA again cites Burghuber, et al. (Ex. 8-40) and Davis, et al. (Ex. 8-80), which as noted repeatedly above are very weak, especially relative to the scientific weight OSHA is urging them to carry.

OSHA claims that effects of ETS exposure "may be additionally aggravated by simultaneous exposure to other compounds." In support, OSHA cites Ex. 3-446, which consists of comments from a government employee's labor union, and appears to provide no substantive information on this issue. On this same point, OSHA cites a 1988 review by Eriksen, et al. (Ex. 8-99) This

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is perplexing, since the conclusions in Ex. 8-99 generally track those in the 1986 National Research Council and Surgeon General's Reports, namely, that data on the issue of ETS exposure and cardiovascular effects are methodologically weak and unconvincing.

There are several reports and reviews, not considered or not adequately taken into account by OSHA, which have addressed the issue of potential cardiovascular responses to ETS. Selections from this literature are set forth in Part II.C. of this submission, indicating a sizeable body of scientific data and opinion questioning a role of ETS or of ETS constituents in acute cardiovascular effects.

OSHA's discussion of epidemiologic and experimental data does not adequately support claims of an increased risk of chronic heart effects associated with ETS exposure in the workplace; OSHA fails to critically review cited studies; OSHA misrepresents the nature of available data

OSHA addresses the issue of chronic heart effects in the Proposed Rule at Section II.C.4.(e). (59 FR 15978-9) Epidemiologic literature on this issue is also reviewed in the context of its risk assessment, at Section IV.B. (59 FR 15992)

In Section II.C.4.(e), OSHA provides a single paragraph discussion of the epidemiologic studies relating to ETS and heart

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disease, coming to the conclusion that these studies indicate a "modest impact" of ETS exposure on heart disease, with relative risks in the range of 1.3 to 2.7.

OSHA cites the following epidemiological reports.

Ex. 8-85, Dobson, et al. (1991)

Ex. 8-120, Garland, et al. (1985)

Ex. 8-138, He, et al. (1989)

Ex. 8-139, Helsing, et al. (1988)

Ex. 8-142, Hirayama (1984)

Ex. 8-148, Hole, et al. (1989)

Ex. 8-154, Humble, et al. (1990)

Ex. 8-191, Lee, et al. (1986)

Ex. 8-277, Sandler, et al. (1989)

Ex. 8-295, Svendsen, et al. (1987)

Contrary to OSHA's claim, the 11 citations given by OSHA in support of its conclusion do not report a consistent association of ETS exposure, usually inferred from spousal smoking, and heart disease risk. In studies where questionnaire estimates were obtained concerning workplace exposure, the data are especially weak on the issue of a possible association of ETS exposure and heart disease risk.

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OSHA's misleading use of the 11 epidemiologic reports it cites on ETS and heart disease is evident in the manner in which these reports are grouped in Table IV-2. (59 FR 15993) In two instances, once in the "Positive" column and once in the "Equivocal positive trend" column, OSHA cites the same study twice. In the "Positive" column, both Helsing, et al. (Ex. 8-139) and Sandler, et al. (Ex. 8-277) provide essentially the same data on ETS and heart disease. In the "Equivocal positive trend" column, Gillis, et al. (Ex. 8-122) report preliminary data later reported by Hole, et al. (Ex. 8-148) Listing all four reports, when only two studies are represented, gives the impression that more "positive" data are available than in fact might be the case.

It is of special interest that two of the studies on ETS and heart disease cited by OSHA as "positive" or with an "equivocal positive trend" reported data using questionnaire estimates of workplace exposure. However, neither of these studies provides data suggesting an association of workplace ETS exposure and increased heart disease risk.

One of the studies with workplace data, Dobson, et al. (Ex. 8-85), is categorized by OSHA in Table IV-2 (59 FR 15993) as "positive." However, in this study, for ETS exposure at work, the odds ratios and 95% confidence intervals were 0.95 (0.51-1.78) for men and 0.66 (0.17-2.62) for women. Dobson, et al. concluded:

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"The odds ratios for passive smoking at work did not suggest increased risk." (p. 793)

In another report, categorized by OSHA as having an "equivocal positive trend," Svendsen, et al. (Ex. 8-295) collected a "limited amount" of data on workplace ETS exposure. Study participants were asked about the smoking habits of their coworkers. Comparing nonsmokers whose coworkers smoked to nonsmokers whose coworkers did not smoke, the following relative risks (with 95% confidence intervals) were reported for heart disease.

-- Coronary heart disease death - RR = 2.6 (CI 0.5-12.7)

-- Fatal or nonfatal coronary heart disease - RR = 1.4 (CI 0.8-2.5)

Svendsen, et al. also reported data on a potential joint effect of coworker smoking plus spousal smoking, for the endpoint fatal or nonfatal coronary heart disease. Relative to nonsmoking men, neither whose wives nor coworkers smoked, the following risks were reported.

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-- Both wife and coworkers smoked - RR = 1.7 (CI 0.8-3.6)

-- Wife smoked, but coworkers did not - RR = 1.2 (CI 0.4-3.7)

-- Wife did not smoke, but coworkers did - RR = 1.0 (CI 0.5-1.9)

In sum, all relative risks pertaining to workplace ETS exposure (either alone or in combination with spousal smoking) were not statistically significant.

OSHA incorrectly lists Hirayama (Ex. 8-142) as a "positive" study in Table IV-2. (59 FR 15993) While one of Hirayama's tables (Table 5, p. 183 of Ex. 8-142) appears to contain a statistically significant risk ratio for one subgroup of nonsmoking women married to smokers, Hirayama did not report an overall relative risk. Using Hirayama's data, however, Lee (Lee, P.N., Environmental Tobacco Smoke and Mortality. Karger, New York, 1992) recently calculated this ratio to be a nonstatistically significant 1.15 (95% C.I.: 0.94-1.42). (Lee, 1992, p. 187)

Very little weight can be given to the He, et al. study (Ex. 8-138), since it is a minor Chinese-language report based on

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only 34 heart disease cases. As noted previously, the Sandler, et al. (Ex. 8-277) report is not relevant since it repeats the data in Helsing, et al. (Ex. 8-139) Also, as noted, the Dobson, et al. report (Ex. 8-85), actually reported nonstatistically significant relative risks less than 1.0 insofar as workplace data are concerned. This leaves OSHA's conclusions on increased heart disease risk based on a single "positive" epidemiological study, Helsing, et al. (Ex. 8-139)

As is typical of ETS epidemiological studies, Helsing, et al. suffers from weaknesses, such as unreliable ETS exposure estimates, and failure to attempt to control for confounding factors. The issue of unreliable exposure estimates is a particular problem for Helsing, et al., because the smoking status data were collected in 1963 and then used to classify subjects during the 12 years following. Many changes probably occurred in smoking behavior during the subsequent 12-year follow-up. This concern was noted by the authors.

> All smoking data were obtained in the 1963 census, so no provision can be made for changes in smoking habits which we know took place as a result of publicity about health effects of smoking. (p. 921)

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Other changes in the compositions of the households may have occurred during the follow-up period. Although the authors

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assume that any changes might influence the ETS comparison groups randomly, this is mere speculation.

> We also have no data on changes in the household composition which may have occurred prior to or after 1963. Thus, we implicitly assume that any such changes occurred randomly in the population. (p. 921)

Although an attempt was made to adjust statistically for some potential heart disease risk factors (age, sex, etc.), no data were available on many potentially important risk factors for heart disease, such as diet, exercise, blood pressure and cholesterol.

> We have very little data on other risk factors for arteriosclerotic heart disease in the study population. . . . other factors such as diet and exercise might differ in families with and without smokers; we cannot ignore the possibility that such differences could influence our findings. (p. 921)

In sum, the epidemiological literature cited by OSHA as providing "positive" evidence of an ETS and heart disease association provides an extremely weak scientific basis for such a claim. After excluding incorrectly cited literature (Sandler, et al.; Hirayama), a small-scale foreign report of uncertain reliability (He, et al.) and research which, in fact, challenges a workplace ETS exposure/heart disease claim (Dobson, et al.), OSHA

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is left with a single supporting citation (Helsing, et al.), which itself is highly flawed.

The problems with Helsing, et al. are particularly troublesome for OSHA's case, because OSHA's risk estimate for heart disease deaths associated with ETS (Section IV.D., 59 FR 15995-6), depends entirely on the Helsing, et al. data for its relative risks. OSHA ignores or glosses over the study's weaknesses relating to ETS exposure, classification of smoking status and confounding factors. Furthermore, without adequate foundation, OSHA states matter-of-factly that the Helsing, et al. study "can be generalized to the general public," conveniently failing to acknowledge that the Helsing, et al. study was performed in a single county in a single state in the U.S.

In addition to epidemiologic reports, OSHA also uncritically cites a number of laboratory and clinical reports or reviews, many of which were designed to examine active smoking and do not even relate to ETS. Other studies which purport to relate to ETS are cited by OSHA as fact without any serious attempt to evaluate their scientific validity.

For example, OSHA provides a substantial amount of detail concerning a recent study said to show that ETS exposure increases myocardial infarct size in rats and increases atherosclerosis in

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rabbits. In this context, OSHA incorrectly describes a 1993 report by Zhu, et al. (Ex. 8-330) as relating to infarct size in rats, when, in fact, Ex. 8-330 is a rabbit study of atherosclerosis. The rat infarct study described by OSHA appears to be a 1994 report by Zhu, et al. (Zhu, B., Sun, Y., Sievers, R.E., Glantz, S.A., Parmley, W.W. and Wolfe, C.L., "Exposure to Environmental Tobacco Smoke Increases Myocardial Infarct Size in Rats," Circulation 89(3): 1282-1289, 1994.) Neither the 1994 Zhu, et al. report on rat infarcts, nor the report on atherosclerosis in rabbits cited by OSHA (Ex. 8-330) meet basic standards of scientific control. Both involve excessively high levels of smoke exposure, which was sidestream smoke, not ETS. The conditions of exposure also left a stress factor uncontrolled, which is particularly important in heart disease research.

To examine the 1994, Zhu, et al. report in more detail, it is clear that it is not even relevant to ETS. It apparently involved simultaneous exposure of groups of rats, up to 24 at a time, to extremely high levels of sidestream smoke, not ETS, in an unventilated exposure chamber. The average air levels of nicotine (1103 $\mu g/m^3$) and carbon monoxide (92 ppm) are several orders of magnitude higher than would be observed in even the most extreme human smoking situation. Moreover, a group of confined rats together in a chamber pumped full of smoke to the point where breathing was almost impossible is going to experience stress in

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direct proportion to the extent of exposure. Any test for myocardial infarction is going to be influenced by such a stress factor. In short, the Zhu, et al. study is probably more of a study of stress than a study of ETS.

In an effort to support OSHA's claim that ETS adversely affects "blood components," OSHA denotes nearly half a column to a 1985 report by Olson. (Ex. 8-245) Olson reports that excessive exposure to intense levels of only weakly diluted sidestream smoke in rats can substantially elevate COHb levels. However, the Olson report did not even pertain to heart disease; it was a study of lung enzymes. It involved high concentrations of sidestream smoke, not ETS, which is a highly dilute mixture. Furthermore, it is clear that the exposure conditions were not relevant to COHb levels associated with ETS, when even literature cited by OSHA indicates that COHb levels in ETS-exposed nonsmokers are essentially indistinguishable from nonexposed nonsmokers. (Guerin, et al., Ex. 8-129, discussed under "Acute Effects.")

The Davis, et al. report (Ex. 8-80) on platelets and endothelial cells is again cited, despite its lack of an adequate control condition.

OSHA cites two Czechoslovakian reports to support a claim that ETS exposure affects cardiac cellular metabolism.

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(Gvozdjakova, et al., 1984, Ex. 8-130; Gvozdjakova, et al., 1985, Ex. 8-131) Both of these studies are from the same laboratory and involve an experimental model in which rabbits were apparently exposed to mainstream cigarette smoke for periods of up to eight weeks. The authors claim that this smoke exposure adversely effected myocardial mitochonchial respiration. This is suggested as a mechanism underlying cardiomyopathy in smokers. Although the model involved "passive" inhalation of smoke by the rabbits, it is clear from the levels and nature of smoke delivery, and from the authors' explicit comments, that this research was intended to apply directly to heart disease in smokers, not to ETS.

Benowitz (1991) (Ex. 8-25) is cited several times to support claims about nicotine and carbon monoxide. This citation, however, does not deal with ETS. It is a review of nicotine in the context of smoking and delivery of nicotine via nicotine gum or via transdermal patches. Likewise, the Muscat, et al. (1991) report (Ex. 8-234) on lipid profiles deals with smokers, not ETS.

Leone, et al. (1991) (Ex. 4-196) is cited as support for a claim that CO decreases ventricular fibrillation threshold. The Leone, et al. report did not provide data on ventricular fibrillation, much less any data about CO and ventricular fibrillation in particular.

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Conclusion

In conclusion, OSHA's discussion of cardiovascular effects is replete with incorrectly cited literature, misinterpreted or uncritically-examined studies and blatant errors as to the relevance of OSHA's citations to the claims advanced. Thus, OSHA has failed to make its case that ETS exposure in the workplace is associated with heart disease risk. The best available evidence is data on workplace ETS exposure and heart disease risk. To the extent that workplace ETS exposure data are available, an association with heart disease risk is not supported.

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Part II: Additional Literature Ignored or Not Considered Adequately by OSHA

OSHA OMITS A NUMBER OF RELEVANT REVIEWS AND STUDIES FROM THE PROPOSED RULE; THESE REFERENCES FURTHER UNDERMINE CLAIMS THAT ETS EXPOSURE IN THE WORKPLACE IS ASSOCIATED WITH A SIGNIFICANT RISK OF HEART DISEASE

A. Literature reviews challenging claims of ETS-associated risk

The literature contains several literature reviews which conclude that a potential relationship of ETS exposure and heart disease has not been established. In view of the highly limited data on workplace ETS exposure, it is not surprising that none of these reviews provide conclusions specifically focusing on the workplace. However, these reviews do address broad problems with the ETS/heart disease data. If such data are generally inconclusive, then they are reasonably viewed as also specifically inconclusive in regard to the workplace. OSHA failed to recognize the conclusions of these reviews.

U.S. Department of Health and Human Services (1986)[1]

This review examined the available data and judged that "no firm conclusion" (p. 10) could be made regarding a possible relationship between ETS and heart disease.

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Committee on Passive Smoking, Board on Environmental Studies and Toxicology (1986)[2]

This committee report stated that any potential heart disease risk related to ETS would be "difficult to detect or estimate reliably" from epidemiological studies, and would be "the same order of magnitude as what might arise from expected residual confounding due to unmeasured covariates." (p. 263)

Wexler, L.M. (1990)[3]

At a ETS conference held at McGill University in 1989, Lawrence Wexler, of the New York Medical College, concluded that recent data did not provide a basis for altering the earlier conclusions by the Surgeon General and National Research Council concerning ETS and cardiovascular disease.

> Based on the available evidence, it is this author's opinion that it has not been demonstrated that exposure to ETS increases the risk of cardiovascular disease. (p. 139)

Weetman, D.F. and Munby, J. (1990)[4]

Two scientists from the University of Sunderland, United Kingdom, reviewed the literature on ETS and heart disease and presented their conclusions at an international conference on indoor air quality held in Lisbon, Portugal in April 1990.

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> It is concluded that no increased risk of cardiovascular disease can be associated unequivocally with exposure to ETS, and it seems probable that this will continue to be the case until specifically designed trials are instigated, and some objective measure of degree of exposure can be devised. (p. 215)

Weetman, D.F. (1993)[5]

In a subsequent conference, which addressed a variety of reported risk factors for heart disease in nonsmokers, Professor Weetman again reviewed the ETS and heart disease issue. His review focused on the epidemiological literature, and emphasized that major flaws in the available studies made it impossible to draw conclusions as to any possible association of ETS exposure and heart disease.

> It is not possible to conclude that a risk to cardiovascular health has been established from the epidemiological studies considered in this paper. Each of the studies is flawed in at least one major way. If there are to be more studies, and the importance of cardiovascular diseases suggests there should be, one can only hope that they will be conducted in a careful and objective way. (pp. 134-135)

Thiery, J. and Cremer, P. (1990)[6]

Two physicians from the University of Munich, Germany, presented their conclusions at an international conference in Hungary in June 1990.

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> Taking into account the small increase in coronary risk in passive smokers as compared to non-exposed subjects and also the low validity and small number of epidemiological studies available and the fact that their results are at least inconsistent, a relationship between passive smoking and cardiovascular diseases cannot be established on these data. (p. 6)

Armitage, A.K. (1991)[7]

In a 1991 book discussing a wide range of issues involving ETS, the literature on heart disease was reviewed by Alan Armitage, former director of toxicology of a major European research laboratory and head of pharmacology at the Tobacco Research Council Laboratories in the United Kingdom. He judged that the scientific data have not established an increased heart disease risk in nonsmokers exposed to ETS.

> It is clear that the evidence for a harmful effect of ETS in enhancing CHD [coronary heart disease] risk in non-smokers is not very convincing. . . . (p. 114)

Armitage, A.K. (1993)[8]

In a subsequent review in 1993, Armitage, writing as a consultant pharmacologist and toxicologist, expressed a similar evaluation of the ETS/heart disease literature.

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> On the current evidence a causal relationship between exposure to ETS and the development of CHD has not been proved. (p. 27)

Caldwell, A.D.S. (1993)[9]

Armitage's 1993 review appeared in the Journal of Smoking-Related Diseases. In an editorial in the same journal issue, A.D.S. Caldwell, the journal's managing editor, emphasized that the issue of confounding variables was of particular importance in the case of heart disease. This is because of the hundreds of factors reportedly associated with the disease. Caldwell observed that the numerous heart disease risk factors make it extremely difficult to make confident statements about a potential role of ETS.

> But assessing the impact of ETS is an exercise made hazardous by confounding variables lurking around every statistical corner. In the case of CHD, for example, some 300 risk factors have at some time or other been identified -- by what means is it possible to unravel these data and point the finger with any degree of confidence at ETS per se as a major causative element?

Lee, P.N. (1991)[10]

In 1991, Peter Lee, an independent British statistical consultant, published a critical analysis of the epidemiological literature relating to ETS exposure, cancer and heart disease. In the area of heart disease, he was particularly critical of the risk

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assessments by Wells (1988) and Kawachi, et al. (1989). Both of these risk assessments concluded that ETS is associated with a large number of heart disease deaths annually. Lee challenged this conclusion, and agreed with the 1986 National Academy of Sciences and Surgeon General's reports, in that both considered the ETS/heart disease data inadequate.

> In the risk assessment by Wells, heart disease deaths formed 70% of the total. In that by Kawachi et al, they formed 89%. As noted above, in 1986 none of the major authorities considered that ETS had been shown to cause heart disease. Evidently Wells and Kawachi, in assuming that ETS causes heart disease, are jumping to a conclusion that a number of panels of distinguished scientists have not reached. While there are more data now than in 1986, it remains abundantly clear that the evidence still does not support this conclusion. (p. 199)

> Although it has been demonstrated above that the risk assessment for heart disease essentially rests on the results from two studies, both of which seem unreliable, a number of other general points can be made. First, there are a very large number of risk factors for heart disease. It is evident that adjustment for these factors in the studies has always been incomplete, and often seriously incomplete. Second, the extent of the association seen in some of these studies, which in some cases is close to that reported in relation to active smoking, is implausibly high when viewed against the extent of the association seen in relation to active smoking. Third, there is a major danger of publication bias. It is notable that the literature is still relatively sparse despite the numerous ongoing studies of heart disease and the fact that heart disease in a non-

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> smoker is probably 50 times or so more common than lung cancer in a non-smoker. (p. 200)

Lee, P.N. (1992)[11]

In 1992, Peter Lee published a more detailed, book-length review of the epidemiological literature on ETS exposure in relation to mortality and several diseases. In his view, various weaknesses and biases in the data precluded the ability to draw any conclusion as to the potential association of ETS exposure and heart disease.

> Mainly because of the problems caused by the strong likelihood of severe publication bias, it cannot be concluded from the existing evidence that ETS is associated with heart disease. The present author understands that the American Cancer Society intends to publish within the next year or so findings related to ETS based on its second large prospective study. It is hoped that results from its first prospective study will also be released. Until there is such evidence, and hopefully also evidence from other studies involving substantial numbers of deaths from heart disease with good control of confounding and with evidence on ETS exposure from sources other than the spouse or in the home, it is certainly premature to come to any conclusions. (pp. 195-196)

Huber, G.L. Brockie, R.E. and Mahajan, V.K. (1992)[12]

Gary Huber, M.D., of the University of Texas Health Center, in collaboration with two other physicians, recently reviewed the literature relating to claims that ETS is associated

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with increased heart disease risk. These authors described the epidemiological studies as "inconsistent" and considered the magnitude of the risks reported in these studies to be "within the range of 'background noise.'" Huber, et al. also emphasized the point that potential confounding variables have not been adequately controlled in studies of ETS exposure and heart disease.

> The studies should be viewed with healthy scientific skepticism because they have not been controlled adequately for numerous confounding factors potentially important to the development of these diseases. (p. 32)

Aviado, D.M. (1992)[13]

In 1992, Domingo Aviado, M.D., a consultant with Atmospheric Health Sciences in Short Hills, N.J., published an extensive review of environmental tobacco smoke in the context of heart disease in the workplace. He did not consider the data supportive of an association of workplace ETS exposure with heart disease, and emphasized the low levels of ETS constituents to which workers might be exposed.

> It is the opinion of this author that the available studies do not support a judgment that ETS exposure is associated with any form of occupation-related heart disease. Although ETS reportedly contains constituents that have been associated with occupational heart disease, the concentrations are so low that it is unlikely for any substance to attain the

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corresponding TLV (threshold limit value) in a work environment. (pp. 475-476)

Aviado, D.M. (1993)[14]

In 1993, Dr. Aviado again addressed this issue, concluding that "the available studies do not support a judgment that ETS exposure is associated with any form of occupation-related heart disease." (p. 130)

Crépat, G. (1992)[15]

G. Crépat, a scientist at the University of Dijon, France, reviewed the literature relating to ETS exposure and heart disease, in a presentation at an international indoor air quality meeting in Athens, in April 1992. He concluded that the relative risks for ETS and heart disease reported in epidemiologic studies have probably been overestimated and are not explained by the available "physiobiochemical" data.

> This suggests that mean RR [relative risk] of CHD due to ETS exposure calculated from available epidemiologic studies, has probably been overestimated as at the moment it cannot be explained by physiobiochemical changes caused by ETS in the body. (p. 440)

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B. Literature emphasizing low levels of ETS constituents

One way to approach the question of ETS and heart disease is to examine the levels of ETS to which nonsmokers might be exposed. Reported levels of exposure to carbon monoxide may be particularly of interest in view of the potential role some authors have speculated it to have in heart disease. The literature provides many examples of reviews concluding that potential nonsmoker ETS or CO exposure levels are extremely low and not likely to be of physiological significance. The conclusions of several notable examinations of this issue are extracted below.

Adlkofer, F.X., Scherer, G., Von Meyerinck, L., Von Maltzan, Ch. and Jarczyk, L. (1989)[16]

> COHb in passive smokers rises only slightly above the normal physiological level so that it is difficult to differentiate from COHb-values measured in non-exposed non-smokers. (p. 185)

Cole, P. (1981)[17]

> Another source of CO is the inhalation of exhaled tobacco smoke and sidestream smoke from other smokers, called 'passive smoking'. In a City office adjacent to Barts, where smoking was allowed, we measured the COHb levels in 100 non-smokers working alongside active smokers. Again, the mean level was slightly up, 1.12%, but again the increase is hardly significant. Passive smoking, although undeniably unpleasant to some can hardly be described as a health hazard. The rise in COHb does not even approach that found in an

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active smoker. In the same City office we measured COHb in a 100 active smokers at the same time. They showed a mean level of 5.5% with a maximum of 13%, a completely different picture. We have rarely found a known non-smoker to exceed a level of 2.5% COHb and most are much lower. (p. 76)

Gori, G.B. and Mantel, N. (1991)[18]

The daily levels of cigarette consumption compatible with no significantly increased risk for other diseases associated with active smoking appear to be of the same order as for lung cancer. Tables 4 and 5 report the analogous estimates for cardiovascular and respiratory disease mortality, with the implication that retained doses of ETS are unlikely to be associated with significant risk elevations for such disease as well. (p. 96)

Table 4 in the paper summarizes data from epidemiologic studies of smoking and heart disease, and provides the "maximum levels of daily cigarette consumption at which risk for coronary heart disease mortality in male smokers may not be significantly increased from the risk of nonsmokers." The maximum levels are in the range of 1.5-4.5 cigarettes per day. By contrast, Gori and Mantel calculate that the average ETS-exposure for a nonsmoker is "less than one cigarette over the course of 1 year."

Together, these considerations suggest that the lung cell doses for average ETS-exposed nonsmokers are probably between 1/10,000 and 1/100,000 of equivalent cell doses for average mainstream active smokers. In practical

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terms, this implies an annual retained dose of tobacco smoke components equivalent to far less than the dose from the active smoking of one cigarette somehow evenly dispersed over a 1-year period. (p. 94)

Malmfors, T., Thorburn, D. and Westlin, A. (1989)[19]

This is a study of the air quality in passenger aircraft, focusing on components related to ETS. Although no potential health effects were measured, the report emphasizes the low levels of ETS-related components, and observes these are unlikely to have an important cardiovascular significance. It is also noted that the nicotine and carbon monoxide levels in aircraft cabins are well below the standards set by OSHA.

It can be seen that the nicotine concentrations found in the present study are roughly one-tenth of the standard for the working environment set by OSHA. The concentration of carbon monoxide is also about one-tenth of the standard for general indoor air and even less for the working environment. (p. 623)

From this comparison it appears that the quality of the aircraft cabin air in the present study is satisfactory and better for factors related to ETS - nicotine and carbon monoxide - than for carbon dioxide and relative humidity. (p. 624)

Any effects on the cardiovascular system would have been mostly unnoticed in healthy individuals, because there are no known direct effects of ETS on the cardiovascular system beyond the formation of carboxyhemoglobin. The latter is so minimal that it will not affect the cardiovascular function. (p. 626)

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Proctor, C.J., Warren, N.D., Bevan, M.A.J. and Baker-Rogers, J. (1991)[20]

It seems that the main factor in exposure to environmental tobacco smoke is living with a smoker. Exposure at work, leisure, or travel seems to be minor. Overall, exposure to airborne nicotine was found to be low (mean 2.3 $\mu g\ m^{-3}$, median $<0.1\ mg\ m^{-3}$). (p. 296)

Mennear, J.H. (1993)[21]

The role, if any, of environmental tobacco smoke (ETS) in the causation and/or exacerbation of cardiovascular disease remains to be proven and defined. . . . The findings show that there is scant clinical or experimental evidence to support a role for carbon monoxide in the causation of ischemic heart disease. Further, the results of field studies of relative air quality in nonsmoking and smoking homes, offices, and public places show that ETS contributes only minor and toxicologically insignificant increments in ambient carbon monoxide concentrations. These increments are variable and easily masked by other common carbon monoxide sources such as internal combustion engines and the burning of cooking and heating fuels. It is concluded that if ETS plays a role in the etiology of cardiovascular disease, it is most likely not mediated through carbon monoxide. (p. 77)

Roe, F.J.C., (1993)[22]

Although it has not been proven that intermittent low peak levels of COHb do no permanent harm, it seems likely that the healthy body can compensate for them completely. (p. 120)

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There is no clear evidence that exposure to CO is associated with an increased incidence of any form of cardiovascular disease. (p. 125)

Rylander, R. (1983)[23]

The unimportance of carbon monoxide has been further confirmed. . . . CO from ETS is not important from a health point of view. (p. 144)

Schievelbein, H. and Richter, F. (1984)[24]

Cardiovascular effects of tobacco smoke have been studied in passive smokers far less extensively than in active smokers. Under real-life conditions, passive smokers inhale approximately 0.02 to 0.01 of the amount of particulate matter taken up by active smokers. Their nicotine concentration in serum is within a range that is barely distinguishable from the background level. The increase in carboxyhemoglobin rarely exceed 1%. In healthy subjects heavily exposed to tobacco smoke, no or only slightly acute effects on the cardiovascular system are found. Whether or not passive smoking is likely to aggravate symptoms in patients with advanced coronary heart disease has not yet been unequivocally established and requires further investigation. From a few studies on occupational groups exposed to carbon monoxide (CO) and from experiments with animals chronically treated with CO or nicotine, the conclusion can be drawn that neither CO nor nicotine is likely to play a role in the development and progression of coronary heart disease in those concentrations normally found in passive smokers. (p. 626)

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C. Literature emphasizing that any measurable acute cardiovascular responses to ETS are minor

(1) Healthy subjects

Several aspects of cardiovascular function, such as heart rate and blood pressure, can be readily measured in laboratory studies. Even if short-term changes in such parameters were consistently reported following acute exposure to ETS or CO, their potential clinical significance is highly uncertain. On the other hand, if the literature does not consistently report important acute cardiovascular responses, this further undermines claims of a potential relationship between ETS and heart disease.

A number of studies and reviews have examined potential acute cardiovascular responses to either ETS or CO. A sample of this literature is cited below, indicating a sizeable body of scientific data and opinion questioning a role of ETS or CO in such effects.

Committee on Passive Smoking, Board on Environmental Studies and Toxicology (1986)[25]

The report reviews studies of possible acute effects of ETS on the cardiovascular system in healthy subjects, and concludes that there are no significant changes. The report, although avoiding a firm conclusion, expresses that, for angina patients,

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there is a possible cause for concern about exposure to the CO in ETS.

> In summary, for normal young adult males and females, no significant acute effects of ETS exposure on heart rate or blood pressure have been reported, either under resting or aerobic conditions. (p. 260)

Fischer, T., Weber, A. and Grandjean, E. (1978)[26]

Potential subjective, irritant and physiological (e.g., heart rate) effects of ETS were assessed in a laboratory setting. No pulmonary function or heart rate effects were reported. However, the authors nevertheless consider ETS a serious problem in view of irritant effects, potential effects in sensitive persons and levels to which some restaurant and bar employees are exposed.

> Pulmonary function tests should give us an indication of eventual bronchial constriction, encountered frequently in smokers. In fact, our spirometric methods showed no differences before and after exposure to smoke. The change in heart rate during the test was just as insignificant. (uncertified translation, p. 8)

Harke, H.-P. and Bleichert, A. (1972)[27]

> Measurements of electrocardiogram, blood pressure, and puls [sic] frequency showed, that these parameters were not altered by passive smoking. (p. 312)

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Hulka, B.S. (1988)[28]

> Studies of acute ETS exposure in healthy children and adults have shown no statistically significant alterations in heart rate or blood pressure either during resting conditions or during exercise. Studies of ETS exposure in persons with pre-existing atherosclerotic heart disease have been inconclusive. Important questions about ETS exposure and the induction of angina, electrocardiographic abnormalities, and cardiac arrhythmias are unanswered. (p. 537)

International Collaborative Group (1984)[29]

This study examined children (approximately 13 years old) from cities in Germany, Cuba, Hungary and the USSR. Two sample groups were compared, one representing the upper 5% and one representing the remainder of the blood pressure distribution curve. One of the characteristics compared between these two groups was parental smoking habits. No significant association was reported between the children's blood pressure and parental smoking.

> The proportion of smokers among the fathers was slightly higher in the lower (55.8%) than in the upper group (54.7%); this difference was not significant. The proportion of smokers among mothers was, however, significantly higher in the lower than in the upper group ($P<0.01$). The proportion of smoking fathers was lowest in Berlin-Köpenick (46.3% vs. 38.6%) and highest in Havana (66.3% vs. 66.7%). The proportion of smoking mothers was lowest in Moscow 3 (0% vs. 1.4%) and highest in Budapest (29.4% vs. 32.0%). The mean blood pressure values of the children

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showed no significant association with the smoking habits of either parent. (p. 122)

Pimm, P.E., R.J. Shephard and F. Silverman (1978)[30]

It is concluded that in normal subjects the magnitude of physiological responses to acute exposures is minimal. . . . (p. 201)

Rummel, R.M., Crawford, M. and Bruce, P. (1975)[31]

Heart rate and blood pressure measurements were made on 17 male and 39 female nonsmoking college students at 5, 10, 15, and 20 minutes during exposure to exhaled cigarette smoke in an enclosed room. . . . Measurements were correlated with attitudes toward smoke exposure.

For the entire group of nonsmokers, there were no significant changes in heart rate or diastolic blood pressure during the smoke exposure, but systolic blood pressure was significantly increased at 5 minutes of exposure; at 20 minutes of exposure it had returned to preexposure values.

When results were examined according to nonsmokers attitudes, those who "disliked" being exposed had significantly greater heart rates than those who were "indifferent" at all measurements; blood pressures between the two groups did not differ significantly.

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Samet, J.M. (1988)[32]

> While these effects [relating to oxygen transport, heart and blood pressure increases, etc.] of carbon monoxide and nicotine may impair performance, exposures to environmental tobacco smoke are generally at concentrations below which physiological effects would be expected. (p. 12, col. 1)

Shephard, R.J., Collins, R. and Silverman, F. (1979)[33]

The responses of healthy men and women were measured during exercise performance while exposed to ETS vs. a sham exposure. Among several other variables, heart rate was measured. During a preexposure period, those subjects who were to undergo ETS exposure had higher heart rates than the sham subjects. However, actual exposure was associated with a smaller heart rate increase compared to the sham condition.

> The heart rate was higher before the experimental than before the sham exposures. . . . However, while actually exposed to the cigarette smoke both the increment of heart rate and the absolute heart rate were less than in the corresponding sham exposure. (p. 285)

The authors suggested that these heart rate changes might be related to a subjective anxiety or hyperventilation reaction, rather than an actual physiological response to ETS.

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Turner, J.A.McM. and McNicol, M.W. (1993)[34]

In a partially blind randomized control study, nine healthy adult men performed progressive sub-maximal exercise tests, either after chewing nicotine chewing gun (4 mg) or breathing carbon monoxide (320 p.p.m.). Neither agent significantly affected exercise performance, despite a mean rise in blood nicotine to 17.0 ng ml^{-1} during nicotine administration and a COHb rise to 6.9% whilst breathing carbon monoxide. (p. 427)

Weber-Tschopp, A., Fischer, T. and Grandjean, E. (1976)[35]

Thirty three subjects were exposed in a climatic chamber to cigarette smoke (side stream) produced by a smoking machine. . . . $\%FEV_1/VC$, MMF and heart rate were not significantly affected during exposure. (p. 277)

Weber, A., Fischer, T. and Grandjean, E. (1979)[36]

In a first study subjects were exposed for 1 hr to constant cigarette smoke concentrations corresponding to 5 or 10 ppm CO. Annoyance, subjective eye irritations, and eye blink rate increase in both conditions during the first 30 min of exposure. Respiratory frequency and heart rate variability are not altered. (p. 205)

Winneke, G., Plischke, K., Roscovanu, A. and Schlipkoeter, H.-W. (1984)[37]

Neither blood pressure-values, nor heart-rates or fingerpulse-volume were influenced by exposure to tobacco-smoke. This correspond to the fact that nicotine-intake from passive smoking is negligible. Depth and rate of breathing were not altered either. (p. 353)

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> As for carbon monoxide (CO) there was pronounced uptake in terms of COHb for the high exposure-condition only. In absolute terms, however, the measured values correspond to those found in non-smoking urban populations, and are well below levels considered critical for persons with cardio-vascular impairment. (p. 354)

Winneke, G., Neuf, M., Roscovanu, A. and Schlipköter, H.-W. (1990)[38]

Physiological measurements were obtained from nonsmokers, while they were in an exposure chamber in which another individual was smoking. No significant effects were reported for heart rate or blood pressure. The authors reported that "cardiorespiratory variables were not affected by ETS exposure." (p. 173)

> In taking CO as the basis for comparison our cardiovascular findings are consistent with those of others, who, at even higher levels of ETS-exposure did not observe exposure-related increase of either heart-rate or blood-pressure. Nicotine-intake at such ETS-levels is likely to be too low for cardiovascular changes to be expected. (p. 181)

(2) Angina and other heart disease patients

Claims are sometimes made that ETS, or specifically CO in ETS, aggravates cardiovascular disease in people with pre-existing illness. Such claims typically stem from a limited and largely discredited report by Wilbert Aronow that angina patients

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experienced chest pain sooner when exercising in the presence of ETS.[39] However, a closer examination of the literature reveals a body of data that raises questions about whether ETS, or CO at levels reported to be in ETS, has significant adverse cardiovascular effects.

Hinderliter, A.L., Adams, K.F., Price, C.J., Herbst, M.C., Koch, G. and Sheps, D.S. (1989)[40]

> In conclusion, low-level CO exposure is not arrhythmogenic in patients with coronary heart disease and no ventricular ectopy at baseline. (p. 89)

McNicol, M.W. and Turner, McM. (1983)[41]

> There was no change in the mean oxygen uptake at the onset of angina with any intervention. . . . These results are in contrast with previous reports of the effects of smoking and carbon monoxide on exercise performance in angina pectoris. However in all of these other studies a subjective rather than objective end point was used. We suggest that an objective assessment is essential and that oxygen uptake at the onset of angina is useful and relatively easy to measure.

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Shephard, R.J., Collins, R. and Silverman, F. (1979)[42]

This study was an attempt to determine if asthmatic subjects have an increased sensitivity to ETS exposure. Respiratory symptoms, pulmonary function and heart rates were measured. Although some slight effects (e.g., a small heart rate increase) were reported, these were considered to be of "doubtful

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biological importance" and most likely due to an emotional, rather than directly physiological, response to the ETS exposure.

> There was also some evidence of arousal and/or emotional excitement, including a slight tachycardia (at 80-min exposure, $P<0.05$) and a slight increase of forced vital capacity ($P<0.05$ at 90-min exposure). However, dynamic lung volumes . . . were unaltered. . . . Our data thus do not suggest that asthmatic subjects have an unusual sensitivity to cigarette smoke. (p. 392)

> The physiological changes observed in normal subjects during smoke exposure, although occasionally reaching conventional levels of statistical significance, were of doubtful biological importance (Pimm et al., 1978; Shephard et al., 1979a). Findings included some increase of heart rate and respiratory minute volume, probably of emotional origin, a tendency of increase in functional residual capacity and residual volume in some experiments, and small decreases of dynamic lung volumes. The asthmatic subjects also showed emotional reactions to the cigarette smoke, including the tachycardia, and possibly the preexposure increase of FRC and TLC. (pp. 399, 401)

> We would thus conclude that the specific sensitivity of asthmatic subjects is not a major consideration when determining air quality criteria for rooms contaminated by cigarette smoke. (p. 402)

Sheps, D.S., Adams, K.F., Bromberg, P.A., Goldstein, G.M., O'Neil, J.J., Horstman, D. and Koch, G. (1987)[43]

> In conclusion, there is no clinically significant effect of 3.8% COHb (representing a 2.2% increase from resting values) on the cardiovascular system in this study. (p. 108)

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SECTION VII

MATERIAL IMPAIRMENT: IRRITATION

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IRRITATION

THE PROPOSED RULE DOES NOT CORRELATE COMPLAINTS OF IRRITATION WITH ACTUAL WORKPLACE EXPOSURES TO ETS, AND FAILS TO DEMONSTRATE THAT CURRENT ETS EXPOSURE LEVELS IN THE WORKPLACE POSE A SIGNIFICANT RISK OF MATERIAL IMPAIRMENT FROM "IRRITATION"

OSHA's Proposed Rule states that "mucus membrane irritation" is part of "a wide spectrum of health effects . . . associated with exposure to ETS." (59 FR 15973) In support of its claim that ETS is an "irritant," OSHA cites a single summary review of the literature (1986), two studies and six personal testimonials submitted to the RFI docket. (59 FR 15975) The Proposed Rule also lists several substances that have been defined as "irritants" by NIOSH and are reportedly found in tobacco smoke, but it concedes that specific constituents in ETS have not been directly related to irritation effects. (59 FR 15987-8, 15975)

The two studies on ETS and irritation cited in the Proposed Rule do not establish a significant risk of material impairment at current workplace exposure levels. The data in one of the studies cited in the Proposed Rule were collected in Switzerland in the late 1970s, and the high levels of respirable particulate matter reported therein are not relevant to current ETS exposure levels in the U.S. (Ex. 4-317) Moreover, the Proposed Rule does not address the authors' qualifications of the data in the study, i.e.,

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> . . . there is a very poor correlation between the mean pollutant concentrations in each room and the corresponding results of the interview. This means that the measured pollutant concentration in an individual work room does not necessarily allow drawing conclusions on the extent of disturbance and irritations . . . .;
>
> Individual psychological factors (relationship with co-workers, work satisfaction, attitude toward smoking) considerably influence individual evaluation of disturbances and irritations . . . .;
>
> Thus, there is a considerable variance on the side of measurements of chemical and physical properties as well as on the side of subjective perception and feelings.

A second study cited in the Proposed Rule was conducted in Japan in the mid-1980s. (Ex. 4-18) Subjects were exposed to extremely high levels of tobacco smoke in an experimental chamber. The peak level of exposure to respirable particulate matter was nearly 100 times greater than levels encountered in workplace situations where smoking is permitted. The relevance of this experimental study to OSHA's claim about irritation is unclear; Benzene explicitly prohibits OSHA from basing its finding of "significant risk" at "lower levels of exposure . . . using evidence of health impairments at significantly higher levels of exposure." (AFL-CIO v. OSHA, 965 F.2d 962, at *978)

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"Irritation" Defined

In the introduction to its standard governing workplace exposure to air pollutants, OSHA summarizes its authority as follows:

> Some impairments are so slight a discomfort that they are not material and do not provide a basis for regulation. A complaint of minor discomfort, in and of itself, is not material impairment. However, the OSHA Act is designed to be protective of workers and is to protect against impairment with less impact than severe impairment. (54 FR 2332, 1989)

OSHA also states:

> . . . [C]omplaints of minor irritation would not in and of itself constitute material impairment. In addition, OSHA would weigh irritation with physical manifestations more heavily than irritation with purely subjective responses. This does not mean that purely subjective responses would not constitute material impairment. That judgment would depend on the magnitude of the irritation. (54 FR 2362, 1989)

If OSHA is to support its claim that irritation from exposure to ETS is a material impairment, it must demonstrate that exposures bring about something more than subjective responses of minor irritation or annoyance, i.e., it must demonstrate the "magnitude" of the purported irritation effect. OSHA must demonstrate the "extent of the risk posed by individual substances," i.e., that existing exposure levels in the workplace

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pose a significant risk of material impairment (due to irritation). It also must provide an "assessment of the level at which significant risk of harm is eliminated or substantially reduced." (AFL-CIO v. OSHA, 965 F.2d 962, 1992; *974, *979, *975)

OSHA will find little, if any, support for its position in the scientific literature. For instance, the major databases on sick-building syndrome indicate that tobacco smoke is rarely the underlying cause of complaints about irritation and annoyance related to indoor air quality. (Exs. 3-1053, 3-1073, 3-1074). ETS has been identified as a source of claimed discomfort in only two to five percent of a combined total of 1,000 sick-building investigations.[1-3]

Other published investigations of workplace venues report similar results. For example, in 1992, Canadian researchers reported results of a building investigation in which temperature, humidity, dust, nicotine, formaldehyde, volatile organic compounds, and CO_2 were measured.[4] Occupants of the building complained of poor indoor air quality, and a questionnaire evaluation revealed a substantial number of complaints about unsatisfactory thermal conditions, dry air, drowsiness and eye irritation. However, all measured parameters, including temperature and humidity, were within accepted comfort/exposure guidelines. The authors were unable to correlate any single measured environmental parameter

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with complaints or symptoms. They concluded that their investigation "showed that complaints reported by occupants were associated with perceived rather than measured levels of indoor environmental parameters" [emphasis added].

A 1989 report by Hedge, et al. noted that while self-reported exposures to ETS were associated with increases in perceived symptoms of irritation, no significant correlations between actual levels of ETS constituents in the indoor air and symptom prevalence could be established. Moreover, the researchers reported that "passive smoking" was not associated with self-reports of mucus membrane irritation (MMI).[5]

Pimm and co-workers examined the effects of ETS exposures "at levels typically encountered in public buildings" in the late 1970s.[6] Physiological parameters such as lung flow rates, heart rates and blood carboxyhemoglobin levels were measured. The researchers reported that "the magnitude of the changes was small and of questionable biological significance." The authors also observed that "the subjects were also inevitably aware of the presence of the smoke, and the reported reactions may have been influenced by underlying beliefs and attitudes." Subjective complaints of irritation were categorized as "symptomatic" rather than physiological.

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The Proposed Rule rejects the possibility that complaints about indoor air quality, and specifically complaints about ETS, may be mediated by a psychological component. The Proposed Rule suggests only that a "psychological overlay" may be common to complaints related to poor indoor air quality. (59 FR 15970) However, research indicates that the mere visibility or presence of ETS may provoke symptoms and complaints.[7,8] Winneke and colleagues found that aversion to ETS increased the degree of annoyance and irritation reported under experimental exposure conditions.[7] Researchers from the Illinois Institute of Technology in 1992 reported that simple visual contact "with a source of tobacco odors" increased both perceived odor intensity and the number of subjects perceiving tobacco odor.[8]

Other recently published studies have demonstrated the importance of variables such as job stress, including work control, support, possibilities for personal growth and job satisfaction, in the perception of symptoms due to sick-building syndrome.[9,10] The studies suggest that such factors may either be directly related to symptoms as stress reactions, or they may play a role in rendering the individual more prone to react to environmental influences, including perceived exposures to ETS.[9,10]

ETS is easily identified and is often blamed as the cause of complaints of annoyance and irritation, especially among

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individuals who dislike tobacco smoke. However, a workplace that is adequately ventilated with outdoor air effectively addresses and prevents complaints of irritation and annoyance, regardless of the suggested source.[1-3] ASHRAE ventilation Standard 62-1989 was developed in order to minimize potential complaints of annoyance and irritation in indoor environments. The ventilation rates in the Standard specifically address ETS. The Standard's design criteria currently apply to buildings that have been constructed, renovated or remodeled in the U.S. after 1990. Indeed, the Standard is incorporated by reference into OSHA's Proposed Rule on IAQ. (59 FR 16036)

OSHA's Proposed Rule calls for the complete elimination of ETS exposure in the workplace. This proposal, of course, will not eliminate exposure to irritants in the workplace, since precisely the same irritants imputed to tobacco smoke by OSHA are emitted from other sources. (59 FR 15987-8, 15984) Specific irritants reported in tobacco smoke and generated as well from other indoor sources include formaldehyde and other volatile organic compounds such as acetaldehyde, acrolein, etc. 59 FR 15987-8)

The levels of "irritants" found in the indoor air of the nonindustrial workplace typically overwhelm any possible contributions from tobacco smoke. For example, Godish, in his

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review of formaldehyde exposures from tobacco smoke, writes that even under "extreme circumstances, the effect of cigarette smoking on formaldehyde levels in indoor spaces would be negligible.[11] Guerin, et al., similarly conclude that "as such, it has been difficult for many studies to demonstrate consistently elevated levels of formaldehyde due to ETS."[12] (Ex. 8-129, also submitted to OSHA as Ex. 3-499) They also conclude: "Studies of offices, restaurants, train compartments, and public buildings suggest that ETS contributes to the indoor air burden of VOCs but that other sources predominate. Major sources include building materials, furnishings, cleaning products, office machines, gasoline, and combustion sources associated with cooling, heating, and transportation."[12] Clearly, these results indicate that contributions from ETS to ambient levels of "irritants" are minimal and often indistinguishable from background levels. Any potential risk from irritation associated with ETS therefore would be addressed with the implementation of OSHA's own Proposed Rule on indoor air quality (a ventilation-based indoor air quality standard).

The scientific record is devoid of any data suggesting that ETS is an irritant under current workplace exposure levels and/or under conditions of adequate ventilation (e.g., outdoor air rates specified in ASHRAE 62-1989). OSHA's proposal to reduce alleged irritation from ETS through the complete elimination of

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smoking in the workplace is equivalent to the "regulation of insignificant risks." Benzene clearly states that reduction of significant risk is not tantamount to elimination of all "risk," but only the level or range that may be deemed "significant." (IUD v. API, 448 U.S. 649-651) OSHA has failed to determine any level of that purported "risk."

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SECTION VIII

MATERIAL IMPAIRMENT: PULMONARY EFFECTS

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PULMONARY EFFECTS

OSHA DOES NOT EXERCISE ANY CONSISTENCY OR PURPOSE IN ITS CITING OF THE PUBLISHED LITERATURE; STUDIES ARE CITED FOR IRRELEVANT OR MINOR POINTS, WHILE PERTINENT DATA FROM THE STUDIES ARE NOT REPORTED OR DISCUSSED; OSHA DOES NOT PRESENT ANY CONCRETE ARGUMENTS TO SUPPORT THEIR CONTENTIONS

This is a consistent problem throughout this section of OSHA's Proposed Rule on IAQ/ETS. It appears as though OSHA chooses irrelevant points from studies so as to be able to reference them, while the pertinent data from the studies are ignored in the discussion. No critical analysis is presented, and OSHA makes no concrete arguments to support its conclusion that there is an association between exposure to ETS in the workplace and pulmonary effects in nonsmokers.

OSHA presents data which are irrelevant to a discussion of potential pulmonary effects in nonsmokers exposed to environmental tobacco smoke in the workplace

OSHA's task is to show that there is a significant risk of material health impairment in nonsmokers exposed to environmental tobacco smoke in the workplace. OSHA, however, bases its "review" of pulmonary effects on one experimental study (Ex. 8-18) in humans as well as on several epidemiological studies (Exs. 8-37, 8-62, 8-148, 8-173, 8-176, 8-178, 8-180, 8-209, 8-210, 8-278, 8-

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295, and 8-321), most of which examined reported exposures to ETS in the home environment. OSHA also discusses several animal inhalation studies. (Exs. 8-322, 8-204, 8-290, 8-104, 8-45, and 8-114) OSHA concludes the following:

> The weight of the evidence shows that exposure to ETS results in decreases in pulmonary function indices and increases in respiratory symptoms in otherwise healthy men and women who are exposed to ETS for periods of 10 or more years. [emphasis added] (59 FR 15977)

Because there are studies available that have examined potential effects of exposure to ETS on the respiratory health of nonsmoking adults in the workplace, those are the studies which should be reviewed and analyzed in this section. OSHA presents no critical discussion of the data available from these studies and makes no scientifically supportable claims regarding causation. Recent reviewers of the pulmonary effects literature (who are affiliated with the International Agency for Research on Cancer) concluded that "on the basis of the available data, no definite conclusion (excluding the acute irritating effect of ETS on respiratory mucous membranes) can be drawn."[1] The reviewers' conclusions were not discussed in the Proposed Rule.

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OSHA relies on an experimental exposure chamber study which did not examine or make any conclusions regarding respiratory endpoints in nonsmokers exposed to ETS

OSHA cites a 1983 study by Asano, et al. (Ex. 8-18) This study was an experimental exposure chamber study of only 20 subjects, including 5 male smokers, 5 male nonsmokers and 10 female nonsmokers. It is unclear why OSHA included this study in the pulmonary effects section, since the study reports on non-pulmonary endpoints such as systolic blood pressure and heart rate. This study is therefore irrelevant to a discussion of potential pulmonary effects in nonsmokers exposed to ETS in the workplace.

OSHA RELIES ON SURVEY REPORTS OF NONSMOKERS WHO LIVE WITH ONE OR MORE SMOKER(S); THESE STUDIES SUFFER FROM IMPORTANT FLAWS, AND DO NOT CONSTITUTE THE "BEST AVAILABLE EVIDENCE" REGARDING POTENTIAL PULMONARY EFFECTS IN NONSMOKERS EXPOSED TO ETS IN THE WORKPLACE

The epidemiological literature upon which OSHA bases its conclusion suffers from a couple of very important problems. First, very few of the studies report on workplace exposures to environmental tobacco smoke, the very issue OSHA is proposing to regulate. Second, the studies contain no actual exposure data. In the majority of studies, the estimation of exposure originates from questionnaire responses of subjects and/or their spouses and co-habitants. Even though the studies suffer from these problems, the magnitude of the reported decrements in pulmonary function in

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healthy nonsmokers reportedly exposed to environmental tobacco smoke, as OSHA itself concedes, is very small and of questionable biological or clinical significance.

Among the epidemiologic studies OSHA chose to rely on are several studies of reported home exposures to ETS. The 1985 study by Brunekreef, et al. estimated exposure of nonsmoking women in the Netherlands by asking the subjects to quantify the number of cigarettes smoked daily inside the home by household members. While this study, on cross-sectional analysis, reported that several pulmonary function parameters appeared to be significantly associated with exposure to ETS in the home while others did not, the authors also reported that "there was no association between [ETS] exposure and pulmonary function decline." (Ex. 8-37)

Another study referenced by OSHA, a 1981 paper by Comstock et al., examined reported home exposures of 1,724 adults to environmental tobacco smoke. (Ex. 8-62) The authors of this study, epidemiologists at the Johns Hopkins University School of Medicine, reported:

> The presence of a smoker in the household other than the subject <u>was not associated with the frequency of respiratory symptoms, and only suggestively associated with evidence of impaired ventilatory function</u>. [emphasis added]

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A 1989 study by Hole, et al., is also cited by OSHA. (Ex. 8-148) In this paper, "passive smoking" was defined as living at the same address as a smoker. Additional attempts to quantify exposure involved questioning subjects regarding the number of cigarettes smoked daily by their co-habitee. While this study reported associations between living with a smoker (as a surrogate of ETS exposure) and several respiratory health endpoints in nonsmokers, the 95% confidence interval fell below unity for all respiratory endpoints (i.e., the associations were not statistically significant).

In the Letter to the Editor written by Kalandidi in 1987, which informally reports on a study the author was conducting in Greece that suggested exposure to environmental tobacco smoke "may contribute to the cause of COLD [chronic obstructive lung disease]," the author writes that the studies on exposure to ETS and adult respiratory health contain data that are "equivocal." (Ex. 8-173) In 1990, Kalandidi reported these data in a published paper.[2] While the data were suggestive of a possible association, it is questionable whether the authors adequately considered other potential exposures which have been associated with the development of COLD such as the extremely high levels of outdoor air pollution found in Greece.

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OSHA cites two studies by Kauffman, et al. The first study, published in 1983, reports on home exposures to ETS of nonsmoking women married to smokers. (Ex. 8-176) The second study, published in 1989, reports on similar data. (Ex. 8-178) While the authors reported an association between decreased lung function and "passive smoking" in French women, the authors reported that "no significant association between passive smoking and level of lung function" was apparent in American women. Dr. Michael Lebowitz (a member of the EPA's Science Advisory Board Committee which reviewed the EPA's Risk Assessment on ETS) has questioned the conclusions of the Kauffman study (Ex. 8-176), which, as mentioned above, reported significant differences in lung function between exposed and nonexposed nonsmokers in one part of the study population but no significant differences in the population as a whole. Dr. Lebowitz noted that since the "healthiest" part of the study population lived in the most polluted areas, the study may have been flawed due to biased population selection and testing for other confounding factors.[3]

Since OSHA decided to rely on epidemiologic studies of reported FTS exposures in the home, studies of reported home exposures not cited by OSHA in its proposed rulemaking warrant mention.[4-6] In 1983, for example, Jones, et al., reported that in a case-control study of several hundred nonsmoking women from a U.S. study population, there was no significant association between

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decreases in lung function and exposure to ETS in the home.[4] Similarly, Lebowitz, et al., coordinators of an epidemiologic study of obstructive lung disease in Arizona, reported no association between reported ETS exposures in the home and respiratory health in their adult study population.[5] In a study of 376 families, Yale University scientists Schilling, et al., also reported no evidence that environmental tobacco smoke affects either lung function or respiratory symptoms in adults.[6]

Similarly, OSHA failed to discuss various government reviews of the ETS and adult respiratory health literature which have generally concluded that there is a negligible association, <u>if any</u>, between exposure to ETS and respiratory health effects in adult nonsmokers. For example, the 1986 Surgeon General's report on ETS concluded:

> Healthy adults exposed to environmental tobacco smoke may have small changes on pulmonary function testing, but are unlikely to experience clinically significant deficits in pulmonary function as a result of exposure to environmental tobacco smoke alone.

Other researchers who have analyzed these reported data contend that the results are "mixed and inconclusive." For example, researchers in France, Laurent, et al., have commented that purported long-term health effects from exposure to ETS are difficult to demonstrate in healthy adults and that the results of

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the epidemiological studies are "sometimes conflicting and often open to question."[7] One investigator who is critical of ETS conceded that "the effect of passive smoking on respiratory infections in adults has not been well characterized and reports of its effects on chronic respiratory disease in adults have been inconsistent."[8]

In his summary of the studies on respiratory symptoms and diseases in adults published up to early 1990, American investigator Dr. Philip Witorsch noted that while "4 of 8 [reported] an increased frequency, 4 of 8 [reported] no increased frequency." He stated that, in addition to "all of the problems" with the studies, "these results are too variable to permit any conclusion of association."[9] As his summary demonstrates, the conclusion of the participants at the 1983 U.S. National Institutes of Health workshop on ETS exposure, that the possible effect from ETS "varies from negligible to quite small," is still pertinent.[10]

Thus, OSHA's Proposed Rule has not demonstrated a significant risk of material impairment to health associated with possible pulmonary effects in nonsmokers exposed to ETS in the workplace. Both the literature cited by OSHA and additional material omitted from the Proposed Rule report data which are equivocal and which appear to lack clinical significance.

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THE EPIDEMIOLOGIC STUDIES WHICH EXAMINED REPORTED WORKPLACE EXPOSURES TO ETS IN NONSMOKING ADULTS HAVE REPORTED INCONSISTENT AND INCONCLUSIVE DATA; THE STUDY UPON WHICH OSHA PLACES THE MOST WEIGHT HAS RECEIVED SUBSTANTIAL CRITICISM IN THE SCIENTIFIC LITERATURE FOR QUESTIONABLE DATA ACQUISITION AND ANALYSIS; OSHA FAILS TO ADDRESS ANY OF THESE CRITICISMS

OSHA reports on four studies which contain discussions of workplace exposures to environmental tobacco smoke. Probably the most familiar study mentioned in this section is the 1980 White and Froeb study. (Ex. 8-321) While this study is often cited by individuals in support of an association between exposure to environmental tobacco smoke in the workplace and small airways dysfunction in healthy nonsmokers, the study has received substantial criticism in the published literature. OSHA does not address any of these criticisms in its Proposed Rulemaking.

In regard to the White and Froeb study, a physician at a U.S. medical school questioned their use of carbon monoxide as an index of smoke exposure, contending that they "do not have reliable estimates of the smoke exposure in the environment of their nonsmokers" because it is not unique to tobacco smoke.[11] A British reviewer shared the physician's view that White & Froeb's findings "relate to an index which is contentious and certainly not an accepted reliable indicator of an increased health risk."[12] White and Froeb themselves noted that the average values of the pulmonary

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tests of nonsmokers exposed to tobacco smoke "were not notably different" from the values suggested as normal by a specialist in this area.[13]

Perhaps the most telling criticisms of the study were voiced by Dr. Michael Lebowitz of the University of Arizona at an annual joint meeting of the American Lung Association/American Thoracic Society and in a subsequent letter published in the U.S. Congressional Record.[14-15] During a forum at the ALA meeting, Dr. Lebowitz stated that he had concluded, from his own extensive review of the study and from an interview with White, that the study was "improperly designed" from an epidemiological point of view. He noted that there were problems "inherent" in the study, including the selection of the study group and the measurement of smoke in the workplace. Dr. Lebowitz also expressed concern that the statistical significance of the data appeared to depend on the unexplained omission of data for 3,000 people who were originally included in the study. Based upon these considerations, Dr. Lebowitz urged that the study not be used to support the claim that exposure to ETS in the workplace affects the lung function of healthy nonsmoking adults.

Dr. Lebowitz again took issue with the White and Froeb study in a 1984 paper he presented at the Vienna Symposium on Passive Smoking.[3] He contended:

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> Even with a biased population, poor study design, and incorrect statistical evaluation, there were no clear-cut, consistent, medically meaningful differences between passive smokers and groups of nonsmokers; a corrected statistical analysis strengthened this conclusion.

Fielding and Phenow, whose conclusion that the "changes" reported by White and Froeb were "equivalent to those found in light smokers, who smoke from 1 to 10 cigarettes per day" is reported by OSHA, also made several highly relevant statements that are not mentioned by OSHA. (Ex. 8-102) Fielding and Phenow suggest that the data from the studies on ETS exposure and adults "have been conflicting" and that "taken together, the limited data on the effect of [environmental tobacco] smoke on adult lung function are inconsistent and inconclusive."

In addition to these concerns, the data from the White and Froeb study appear to be inconsistent with other data on lung disease and lung function in nonsmokers. For example, a 1984 study of 1,351 German office workers by Kentner et al., reportedly found no effect of ETS on pulmonary function among exposed nonsmokers. (Ex. 8-180) In a 1988 update of the study, the investigators noted that "there is no evidence that average everyday passive smoke exposure in the office or home leads to an essential reduction of lung function in healthy adults." The key investigator reiterated these conclusions in 1989 and 1990 publications. The 1984 study is

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cited by OSHA in its proposed rule, but no discussion of the study or its data is included.

Two other studies cited by OSHA which report data on workplace exposures of nonsmoking adults to ETS suffer from serious problems regarding exposure assessment. The Masi (1988) study reported on 293 subjects, aged 15 to 35 years old. (Ex. 8-209) The study, however, contains such crude "exposure" data that it is disturbing that OSHA deems it reliable. Workplace "exposure" to ETS was assessed in the following manner:

> Bank employees were asked to [subjectively] assess smoke conditions in the work area as light, moderate, heavy or unable to quantify. . . .[these categories] were arbitrarily converted to number of cigarettes. [emphasis added]

Similarly, the authors of the Masjedi (1990) study conceded that most of their subjects "were unable to quantify the amount of [their] exposure to passive smoke. . ." (Ex. 8-210)

THE EPIDEMIOLOGIC AND EXPERIMENTAL DATA AVAILABLE DO NOT SUPPORT OSHA'S CONTENTION THAT COMPROMISED INDIVIDUALS IN THE WORKPLACE HAVE A SIGNIFICANT RISK OF MATERIAL HEALTH IMPAIRMENT BECAUSE OF EXPOSURE TO ENVIRONMENTAL TOBACCO SMOKE

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OSHA claims that although the pulmonary function decrements reported to be associated with exposure to ETS in

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healthy nonsmokers are small and of questionable clinical significance, these changes may become significant in persons with already impaired pulmonary function (e.g., asthmatics). In its attempt to substantiate this claim, OSHA references two experimental studies on adult asthmatics exposed to ETS for one hour in an exposure chamber. The first study, Knight and Breslin, 1985, reported on only six subjects, four of whom had previously given a positive history of ETS "attacks." (Ex. 8-182) The authors (and OSHA) did not discuss the possibility that psychological factors may have played a role in the subjects' reported "reactions" to the ETS exposure.

The second study, by Dahms et al., 1981, reported on ten patients with asthma (five of whom were included because they reported specific complaints when exposed to cigarette smoke) and ten normal patients. (Ex. 8-76) While the authors reported an association between exposure to ETS and lung function responses in the asthmatic subjects, they reported that "not all subjects showed the same pattern of pulmonary responses to the smoke exposure." The authors also reported that "we were not able to exclude the possibility that these changes in pulmonary function were emotionally related to cigarette smoke" [emphasis added]. Similarly, the 1986 Surgeon General's report recognized that "in this study, subjects were not blinded as to the exposure and were selected because of complaints about smoke sensitivity."

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OSHA also references a 1991 review article by Stanton Glantz and Richard Daynard (Tobacco Liability Project) which makes several claims regarding exposure to environmental tobacco smoke, none of which is supported by a thorough and critical review of the scientific literature available. (Ex. 3-438D)

OSHA claims that asthmatics are believed to be especially sensitive to various environmental influences, including ETS, but a thorough review of the scientific data on ETS does not convincingly support this contention. There are currently ten major studies on ETS exposures among adult asthmatics. Seven of the studies are clinical in nature, where exposures to ETS were controlled under laboratory conditions. The other three studies are population surveys. All of the studies evaluate reports of respiratory symptoms such as coughing, wheezing, and irritation ("subjective complaints") and changes in lung function (an "objective" test for lung impairment).

Only two of the seven clinical studies report objective decreases in lung function among the majority of asthmatics exposed to environmental tobacco smoke. However, the patients in both positive studies were exposed to excessively high and unrealistic levels of ETS [15-32 ppm carbon monoxide], and, as mentioned above, the authors of one of the studies conceded that the observed effects may have been due to psychological factors. In the

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remaining five clinical studies, a number of patients reportedly complained of subjective symptoms upon exposure to ETS, but objective results (i.e., evidence of airways obstruction or significant changes in lung flow rates) were not observed in the vast majority of patients.[16-20]

Data from the three population surveys on adult asthmatics are generally consistent with data reported in the majority of clinical studies.[21-23] A report of a large-scale population survey in the U.S. suggested that ETS exposures in the home did not affect either symptoms or pulmonary function in adult asthmatics. Another group of U.S. researchers recently reported that exposure to ETS did not impair lung function in the 263 asthmatic adult subjects studied. The third study reported mixed results for the development of asthma-related symptoms in individuals reporting exposures to ETS during childhood and adulthood.

OSHA FAILS TO DISCUSS THE PROBLEMS IN GENERALIZING DATA FROM "EXPOSURE CHAMBER" STUDIES TO THE "REAL-WORLD" SITUATION

As mentioned above, the conditions under which asthmatic patients are exposed to ETS in these studies are of questionable relevance to "real-life" exposures. The Surgeon General, in the

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1986 report on ETS, conceded that exposure chamber studies may not be indicative of the "real world" situation:

> Acute exposure in a chamber may not adequately represent exposure in the general environment. Biases in observation and the in [sic] selection of subjects and the subjects' own expectations may account for the widely divergent results. Studies of large numbers of individuals with measurement of the relevant physiologic and exposure parameters will be necessary to adequately address the effects of environmental tobacco smoke exposure on asthmatics.

THE MAJORITY OF ANIMAL STUDIES REFERENCED BY OSHA ARE STUDIES OF MAINSTREAM TOBACCO SMOKE AND ARE NOT RELEVANT TO A DISCUSSION OF POTENTIAL PULMONARY EFFECTS IN NONSMOKING ADULTS EXPOSED TO ENVIRONMENTAL TOBACCO SMOKE IN THE WORKPLACE

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Although OSHA refers to the studies in this section as experimental "ETS" studies, the majority of the studies are mainstream smoke studies which have little or no relevance to ETS issues. ETS is not the same as either mainstream or sidestream smoke. For a complete discussion of this issue, please refer to the section on exposure issues in this submission.

OSHA mentions isolated conclusions from several experimental animal studies but makes no attempt to explain how these data relate to real-life ETS exposures of nonsmoking adults in the workplace. OSHA also does not make any attempt to explain

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the physiological or clinical significance, if any, of the reported data. Nor does OSHA address the apparent inconsistencies in the reported data. For example, "effects" may be reported in one species but not in another.

OSHA makes no attempt to explain the relevance, if any, of these high-dose experiments in animals to real-life workplace exposures in humans, even when some of the studies from which they report data acknowledge that these exposure levels are extreme when compared to the "real world" of "smoke-filled" restaurants or offices. OSHA's responsibility in this proposed rulemaking is to show that workplace exposures to ETS are likely to result in material health impairment in non-smoking adults. They have failed to substantiate this claim.

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OSHA FAILS TO REFERENCE MUCH OF THE RELEVANT LITERATURE SUBMITTED IN RESPONSE TO THE OSHA RFI IN 1992

OSHA presents no critical discussion of potential confounding factors, merely stating that the studies "varied" in their consideration of such factors and that "several studies" have examined isolated variables; OSHA makes no statement regarding the adequacy of control for such factors in these studies

In the Proposed Rule, OSHA presents selected data on the possible association between exposure to ETS and decreased pulmonary function in adult nonsmokers. Philip Morris submitted much of the literature which OSHA has omitted from its Proposed Rule to the docket for the RFI in 1992. (Ex. 3-1074) For a discussion of this literature, please see the response to question 2(a)iii in Ex. 3-1074. A discussion of confounding factors, which OSHA does not provide in its Proposed Rule, is also presented in that section of Ex. 3-1074.

OSHA, while conceding that the studies on ETS exposure and pulmonary effects in nonsmoking adults "vary by numerous factors," makes no apparent attempt to explain why these variations are given no importance in their "analysis" of the literature

OSHA does not elaborate on its statement that the studies on ETS exposure and respiratory effects in nonsmoking adults "vary by numerous factors, such as the population studied, the measures

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used to estimate exposure to ETS, and the physiologic and health outcomes examined." While other reviewers of this body of literature have concluded that it is difficult, if not impossible, to make any definitive conclusions from these data, OSHA attempts, but fails, to make a case for causation.

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SECTION IX

MATERIAL IMPAIRMENT: REPRODUCTIVE EFFECTS

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REPRODUCTIVE EFFECTS

OSHA'S PROPOSED RULE LACKS CONSISTENCY IN ITS DEFINITION OF "ETS EXPOSURE DURING PREGNANCY"

In some instances, OSHA appears to be discussing the potential effects on the fetus that may be associated with active smoking of the mother during pregnancy. At other times, the authors of the Proposed Rule are discussing ETS exposure of the mother during pregnancy. Active smoking of the mother during pregnancy is not synonymous with ETS exposure. OSHA's task is to show that there is a significant risk of material health impairment in fetuses whose mothers are exposed to ETS at work during their pregnancies. The studies referenced by OSHA which examine active smoking during pregnancy are irrelevant to this discussion.

The majority of the studies OSHA references in this section are irrelevant because they deal with active smoking of the mother during pregnancy, not ETS exposure of the mother during pregnancy; ETS and mainstream tobacco smoke are not equivalent

A detailed discussion of the differences between ETS, sidestream and mainstream tobacco smoke is provided in exposure section of this submission.

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OSHA provides a brief, selective and seemingly irrelevant discussion regarding the possible association between workplace ETS exposures of nonsmoking pregnant women and various adverse reproductive outcomes

OSHA claims that "other reproductive effects that have been ascribed to maternal ETS exposure include miscarriage, an increase in congenital abnormalities, and numerous other physiological effects." (59 FR 15979) As references for this section, OSHA provides citations to the Taylor and Wadsworth (1987) study. (Ex. 8-299) This study examined active maternal smoking and reported no data on ETS exposures during pregnancy. OSHA also cites a response to a Letter to the Editor by Ira Tager. (Ex. 8-297) In this letter, Tager makes no mention of "other physiological effects" in infants born to mothers reportedly exposed to ETS during pregnancy and states the following regarding this issue:

> In discussing the harmful effects of passive smoking [during pregnancy], it is important to point out that there is no body of data that absolutely proves that harmful effects will be experienced.

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OSHA also claims that "the effects of environmental [tobacco] smoke exposure on the fetus may have long-term sequelae into childhood and adulthood." (59 FR 15979) The first three studies cited by OSHA make no mention of any purported "effects" of

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ETS exposure during pregnancy on the fetus. (Exs. 8-53, 8-181, 8-213) The fourth study cited by OSHA is a study of active maternal smoking during pregnancy. (Ex. 8-225) OSHA also references a CDC survey which provides no information, conclusions, or data regarding the possible effects of maternal ETS exposure during pregnancy. (Ex. 8-51) Finally, OSHA again cites the response to the Letter to the Editor by Ira Tager outlined above. (Ex. 8-297)

OSHA states that exposure to ETS may be "reflected in the growing child as reductions in lung development" and that "this is especially relevant if that child continues to be exposed to ETS throughout childhood and into adulthood." (59 FR 15979) OSHA again references the Tager letter above to support this point. (Ex. 8-297) It also cites a paper which reports:

> Paternal smoking does not appear to be the environmental exposure leading to both childhood respiratory illness and adult chronic air-flow limitation. [emphasis added] (Ex. 8-177)

OSHA DOES NOT PROVIDE A BALANCED AND COMPLETE DISCUSSION OF THE LITERATURE AVAILABLE, I.E., OSHA FAILS TO MENTION STUDIES WHICH REPORT NO ASSOCIATION BETWEEN EXPOSURE TO ETS DURING PREGNANCY AND ADVERSE REPRODUCTIVE OUTCOMES

In 1992, one group of researchers examined the issue of maternal ETS exposure during pregnancy and spontaneous abortion

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(miscarriage).[1] Although the authors reported that paternal smoking was not associated with spontaneous abortion (after consideration of other independent risk factors), exposure to ETS from sources other than the father was reportedly associated with an increased risk of miscarriage. This is surprising considering that fact that the authors observed no excess risk of spontaneous abortion among "moderate" smoking mothers or among those who actively smoked an average of more than 20 cigarettes per day in the first trimester. The inconsistent and contradictory data from this study appear to be the result of inadequate control for other factors.

Other research has suggested possible associations between maternal exposure to ETS during pregnancy and infant size, premature labor and neonatal asphyxia.[2] In contrast, Savitz, et al., reported that they could provide "no definitive evidence" of an association between paternal smoking and any birth defect.[3] Other authors similarly have reported no associations between maternal exposure to ETS during pregnancy and the incidence of heart defects,[4-5] premature rupture of amniotic membranes,[6] strabismus (an eye disorder)[7] and various other birth defects.[8]

Although several isolated studies have suggested an association between reported exposures to ETS during pregnancy and various conditions in the infant, the data must be considered both

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inconclusive and, in the words of one scientist, "controversial."[9] Another author has suggested:

> Much remains to be done in order to determine whether ETS has any effect on human reproduction or development. Improvements in design of epidemiologic studies of ETS effects, particularly in the areas of exposure assessment and validation and elimination of confounders, are especially important. In addition, appropriate animal studies would be helpful in allowing definitive conclusions to be drawn.[10]

DESPITE THE IRRELEVANCE OF MUCH OF THE LITERATURE OSHA CITES, OSHA STILL FAILS TO PROVIDE A CRITICAL DISCUSSION OF THE PROBLEMS INHERENT IN SUCH EPIDEMIOLOGICAL STUDIES

Probably the most important problems in epidemiologic studies are the lack of quantitative exposure data and the lack of adequate control for potential confounding factors. Exposure estimates in these studies are based on questionnaire information, the validity of which have been questioned repeatedly in the scientific literature.[10] OSHA conveys the impression that confounding factors have been adequately ruled out in these studies. OSHA fails to mention data which, after being adjusted for other factors, have failed to reach statistical significance. The control of confounding variables is of extreme importance in ETS studies examining birth weight. ETS exposure has been shown to "correlate positively with a number of known determinants of

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decreased birth weight," including lower socioeconomic status and poor nutrition.[10] Another group of authors suggests that "it is generally believed that birth weight, perinatal mortality and other measures of reproductive health are sensitive markers of social conditions."[11]

OSHA claims that confounding factors have been adequately ruled out as an explanation for the reported association between paternal smoking and reductions in infant birthweight. OSHA mistakenly arrives at this conclusion by taking factors that were controlled for in a few of the studies and generalizing to the entire population of studies.

In addition to these general problems, there are problems specific to the studies OSHA chose to cite in its Proposed Rule. For example, to support its statement that "data on the reproductive effects due to the exposure of nonsmoking pregnant women to ETS has been presented in many studies," OSHA references two abstracts and six papers. (Exs. 3-438, 8-92, 8-174, 8-208, 8-273, 8-285, 8-287, 8-299) A complete review of the statistical procedures and methods, let alone the data, cannot be performed on abstracts.

There are also problems specific to several of the papers cited by OSHA. For example, the Martin & Bracken paper reported

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that women who were reportedly exposed to someone else's cigarette smoke for at least two hours per day, either at home or at work, during pregnancy delivered infants that were, on average, 24 grams lighter than the infants of women who were reportedly not exposed to ETS. (Ex. 8-208) This relationship was not statistically significant. This paper is also used to provide support for OSHA's statement that "passive exposure to tobacco smoke is estimated to double the risk of low birthweight in a full-term baby." (59 FR 15979) While the authors reported a relative risk of 2.7 (95% confidence interval 1.05-4.50) for a subgroup of the women, when all women with full-term deliveries were included in the analysis there was no statistically significant relationship between reported exposure to ETS during pregnancy and a reduction in infant birthweight. As one author wrote in 1990:

> The analyses reported by Martin and Bracken (1986) are inconsistent and difficult to interpret. This may be due, at least in part, to the authors' use of a relatively crude estimate of ETS exposure. Their findings would have been more meaningful if further information had been available regarding exposure intensity and duration. Further, since questionnaire data were solicited early in gestation, intensity and duration of ETS exposure may have changed considerably for a number of subjects over the remainder of pregnancy.
>
> Potentially important confounders, such as maternal weight and the child's sex, were apparently not determined during the data collection, and thus were unavailable for the

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> analysis, although such variables may significantly influence birth weight.
>
> It is puzzling that the authors used statistical significance as the criterion for inclusion of potential confounders in their multiple regression analyses when, according to various experts, this may eliminate important confounders (e.g., because of low statistical power or multicollinearity).[10]

It should not, then, be surprising that Martin and Bracken conceded that "whether the association found [between decreased infant birthweight and ETS exposure during pregnancy] is due to passive smoking or to some other related factor is unclear" [emphasis added].

The Rubin (1986) paper reported that each pack of cigarettes smoked by the father each day during a mother's pregnancy was associated with a 120 gram reduction in the offspring's birthweight. (Ex. 8-273) However, even a reviewer who is critical of parental smoking, Trichopoulos, has stated that the reported reduction in birthweight reported by Rubin was "extraordinarily large" probably because of poor control for confounding factors.[12] Similarly, another author wrote the following regarding the 1986 Rubin paper:

> An ETS effect of this relative magnitude seems improbable, however, when the relative degrees of exposure are considered. Moreover, in their regression analysis of paternal smoking effects, the authors failed to include interaction terms. This is true even though

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